Economic evaluation in mental healthcare

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Assessing the cost-effectiveness of interventions for patients with major depressive disorder or schizophrenia in the context of the Dutch healthcare system

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Chapter 1

Introduction

Mental disorders are currently acknowledged to be among the most disabling illnesses worldwide. The proportion of the population that will be directly affected by at least one form of mental illness is disturbingly high; lifetime prevalence estimates range from 25% to 41% for Western countries (1, 2). Moreover, it has been indicated that the burden of mental illness will even increase in coming decades (3). Persons with mental illness may present a wide variety of signs and symptoms, and there are large differences between disorders in terms of subjective well-being and impairments experienced in daily functioning. Major depressive disorder and schizophrenia are generally regarded as two of the most disabling forms of mental illness (4, 5). The studies combined in this thesis focus on economic aspects of interventions in patient populations with these disorders.

Main symptoms of *major depressive disorder* include a depressed mood and general loss of interest (6), regularly accompanied by additional symptoms like sleep disturbances, concentration problems, and suicidal ideation or suicide attempts. Depression is associated with high lifetime prevalence rates, estimated at 15% (2), and often runs an intermittent lifelong course with multiple relapses and recurrences (7). Most patients are treated in primary care, where treatment consists of antidepressants and psycho-education. However, management of depression by general practitioners seems to be less than optimal considering the high rate of recurrences and related negative long term consequences (8). An additional complicating aspect for the treatment of depression concerns the limited number of available therapists in secondary care. Consequently, many patients with depression (often with comorbid anxiety disorders) do not receive adequate treatment (9).

Schizophrenia (and related psychotic disorders) is considered to be a complex mental illness that negatively affects fundamental aspects of human functioning. The disorder can be characterised by positive symptoms, including distortions in thinking and perception, and negative symptoms like affective flattening and poverty of speech (6). Estimated prevalence rates range from 0.5% to 0.7% (10). After a first episode of psychosis, guidelines generally recommend the continuation of antipsychotic drugs for at least one to two years following remission. This approach is often successful in preventing relapses, but may also lead to disabling side effects and low compliance. Besides psychopharmacological treatment, care as usual for schizophrenia in the Netherlands consists of psycho-education, support of the patients and their relatives, and individual therapy. Despite the availability of these various treatment options, the majority of patients with schizophrenia continue to have disabling residual symptoms, including persistent auditory hallucinations, and remain handicapped in social functioning.

In addition to the considerable impact of mental illness on the lives of patients, the economic consequences for society are substantial as well. It has been estimated that 1% to 2% of healthcare expenses in Western countries is spent on the treatment of depressive disorders (11, 12), while costs of schizophrenia account for 1% to 3% (11, 13). The extensive use of healthcare resources of patients with depression or schizophrenia is related to the early age at onset in combination with the often chronic (intermittent) course of both disorders (14, 15, 16). The potential financial consequences for society become even more apparent when including costs outside the healthcare sector, like costs of informal care or productivity losses that can be particularly high, especially for patients with depression (12).

In previous decades, decision-makers gradually seem to have become aware of the high disability related to mental illness and the rising costs of mental healthcare. This has resulted in a growing demand for information on both costs and health outcomes to prioritise between alternative interventions and to support reimbursement decisions. However, only few economic evaluations had adequately examined interventions in the area of mental healthcare in the mid 1990s. For most countries and healthcare systems, information on economic aspects was scarce or even absent (17, 18).

Most of the studies available at that time had focused on clinical and economic aspects of psychopharmacological treatment, both in patients with depression (19) and schizophrenia (20, 13). Unfortunately, interpretation of studies on psychopharmacological treatment was generally hampered by short follow-up periods, small numbers of included patients, high drop-out rates, and a narrow scope of included costs. Several economic evaluations had examined psychosocial interventions aimed at depression. Since patients with depression are mainly treated in primary care, studies often compared costs and health outcomes of treatment by general practitioners with outcomes of alternative interventions like cognitive therapy or case management (21, 22). However, clear differences in costs and health outcomes between these interventions and care as usual provided by general practitioners could generally not be found. Detailed economic studies focusing on psychosocial interventions for schizophrenia were scarce, and available results appeared to be inconclusive (23, 24). However, there were indications that interventions like cognitive therapy or behavioural family treatment had the potential to be cost-effective in patients with schizophrenia (25, 26).

In the Netherlands, the importance of economic studies in the area of mental healthcare, and the sheer absence of such studies in the Dutch healthcare system, was recognised in the late 1990s. At that time, the Dutch Ministry of Health, Welfare and Sport had already been stimulating economic evaluations in various

other areas of healthcare. The acknowledged importance of economic studies in mental healthcare resulted in the prioritisation of research on this topic. In the following years, various economic evaluations in mental healthcare were funded by the Dutch National Health Insurance Board (currently CVZ) and ZonMw (Netherlands Organisation for Health Research and Development), including the studies combined in this thesis.

Economic evaluation: a brief overview

Due to scarcity of resources, priorities have to be set for programmes and interventions in all areas of healthcare. Economic evaluation is an important tool to provide information on costs and health outcomes of alternative interventions to decision-makers, and is considered to be essential for rational priority decisions (27).

Most economic evaluations conducted in the area of mental healthcare were designed as cost-effectiveness studies (24, 17). In cost-effectiveness analysis, costs and health outcomes associated with an intervention are used to calculate the incremental cost-effectiveness ratio relative to one or more alternatives (28). Cost-effectiveness studies are generally conducted alongside randomised clinical trials, often comparing newly developed treatment approaches with standard treatment or regular care as provided in the patient population under study. Health outcomes included in cost-effectiveness analysis in mental healthcare are commonly based on disease-specific instruments, instead of generic (preference-based) outcome measures generally recommended by guidelines. For decision-makers, comparisons across disorders or studies are complicated when disease-specific instruments are applied. Since cost-effectiveness analysis requires health outcomes to be expressed in a single (overall) score, some reliable and valid questionnaires that only provide scores on subscales or domains cannot directly be applied in this type of economic evaluation.

In order to assess all the relevant consequences of interventions under study, economic evaluations are preferably conducted from a societal perspective (29). When applying a societal perspective, both medical costs and costs outside the healthcare sector are part of the analysis. Information on the use of healthcare services and other cost aspects is often collected by means of questionnaires (repeatedly) administered to the patients included in a study. Costs are subsequently calculated by multiplying registered quantities with cost prices. In the Netherlands, standard cost prices for frequently used types of costs have been combined in a cost manual, aiming to improve the comparability of studies (30). However, for various services provided in mental healthcare, standard cost prices

are currently unavailable and true costs of resource use have to be estimated in the context of a specific study.
The skewed distribution of costs may lead to methodological and interpretational difficulties, not only in case of analysing cost data, but also when presenting results to decision-makers. Although medians may better represent central tendency in skewed distributions, information on mean costs (and differences in mean costs) is most relevant for decision-makers (31). Nowadays, the bootstrap method (32) is regularly applied to provide information about the uncertainty of economic results. Bootstrap analyses can be used, among other things, to assess confidence intervals surrounding differences in mean costs between groups. Missing cost data may cause difficulties for economic analyses, especially when missingness appears to be not completely at random (33). Since drop-out of patients can be substantial in mental healthcare, it is important to be aware of the potential bias related to incomplete patient data. There are currently various techniques available to handle missing data in economic studies (34).

Aim and overview of the thesis

The main objective of the studies combined in this thesis was to assess the cost-effectiveness of various interventions for patients with mental illness in the context of the Dutch healthcare system. These interventions were primarily aimed at major depressive disorder and schizophrenia, disorders that are associated with serious impairments for patients and considerable costs for society.
C*hapter 2* presents the results of an economic evaluation examining Hallucination focused Integrative Treatment (HIT) in patients with schizophrenia and persistent auditory hallucinations. The HIT programme combines cognitive behaviour therapy with various other treatment modalities, including neuroleptics, coping training, and single family treatment. In previous studies, HIT appeared to be effective in reducing signs and symptoms in various patient populations with auditory hallucinations. The intervention was expected to lead to less intensive healthcare utilisation and lower associated costs, but economic aspects of HIT had not been studied in detail before.
Chapter 3 describes a cost-effectiveness study comparing Cognitive Self-Therapy (CST) with treatment as usual in patients with depression and comorbid anxiety disorders. Previous studies had indicated that self-help interventions can be effective in patients with mental illness. CST is a method that aims to restructure cognitive schemata and address problems in social functioning and relationships. After successfully completing various training phases, patients are allowed to attend CST sessions led by peers. The potential cost savings associated with self-

help interventions like CST seemed particularly relevant for policy makers, but economic studies had rarely been conducted.

Chapter 4 describes the findings of an economic study focusing on a Psycho-Educational Prevention programme (PEP) aimed at primary care patients with depression. Depression is associated with a high risk of recurrence, which not only has negative consequences for patients involved but also leads to considerable healthcare costs. PEP consists of contacts between patients and prevention specialists, educational meetings on depression management, and telephone monitoring. Two enhancements of PEP, i.e. additional psychiatric consultation and cognitive behavioural therapy sessions, were also compared to care as usual provided by general practitioners. In order to register relevant long term outcomes, patients were prospectively followed for three years. This study was the first to examine economic aspects of PEP in a European healthcare setting.

The purpose of the study presented in *Chapter 5* was to examine differences in costs and health outcomes related to alternative medication approaches in patients with first onset psychosis. Guidelines generally recommend maintenance treatment in this patient population, which is successful in preventing relapses but also associated with disabling side effects. Alternatively, guided discontinuation strategy could be applied, in which the use of antipsychotics is gradually decreased, and eventually completely discontinued if possible. This second approach seems less intrusive for patients, but may lead to more relapses. Information on both costs and health outcomes of these medication strategies in patients with first-episode psychosis was required to support policy decisions.

In contrast to most guidelines and recommendations, economic evaluations in mental healthcare are often designed as cost-effectiveness studies that include primary outcome measures aimed at a specific aspect of health. *Chapter 6* presents the difficulties and potentially negative consequences related to the selection of single outcome measures for cost-effectiveness studies in mental healthcare. The various aspects of this topic are illustrated by alternative analyses based on data collected during the HIT study.

Finally, *Chapter 7* discusses the overall findings of the previous chapters, and will provide recommendations for future economic evaluations and related research in the area of mental healthcare.

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Chapter 2

Cost-effectiveness of the HIT programme in patients with schizophrenia and persistent auditory hallucinations

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Abstract

Objective: To examine the cost-effectiveness of Hallucination focused Integrative Treatment (HIT) in patients with schizophrenia and a history of persistent auditory hallucinations.
Method: Costs, in and outside the healthcare sector, and outcomes were registered prospectively during a period of 18 months for patients who received the HIT programme and for patients in the care as usual condition. The Positive And Negative Syndrome Scale (PANSS) was used as main outcome measure in the cost-effectiveness analysis. Bootstrap analyses provided additional information on the skewly distributed costs.
Results: Mean costs per patient in the HIT group ($18,237) were lower than the mean costs per patient in the care as usual group ($21,436). Results of the PANSS were slightly in favour of the HIT group.
Conclusion: There appears to be no significant cost-effectiveness advantage of the HIT programme over care as usual. Additional analyses indicated that future application of the HIT programme will, in most cases, lead to a reduction of (non)medical costs.

Introduction

Schizophrenia is a serious and complex mental disorder with a large impact on the lives of patients and their social environment. As schizophrenia is a chronic condition and patients make intensive use of mental healthcare resources (1), the consequences for national healthcare expenses are substantial as well (2). In recent years, policy-makers have been stimulating the development of interventions and healthcare services that could lead to an improvement in the relation between costs and health outcomes associated with schizophrenia (3-5).

Schizophrenia-related research initially concentrated on the effectiveness of unimodular therapies, in particular medication treatment, but results were generally disappointing (6). It is only for the last decade that the effect of adjunctive treatment, e.g. family treatment (7) and cognitive behaviour therapy (8), has been studied. Adjunctive treatments proved to be more effective as to signs, relapse and rehospitalisation (9). Despite these improvements, the majority of patients with schizophrenia continue to have disabling residual symptoms and remain handicapped in social functioning. Gradually, consensus has been growing that optimal treatment of schizophrenia requires integrative treatment programmes (10), although the exact composition of such programmes remains open for debate.

In 1994, Hallucination focused Integrative Treatment (HIT) was developed at the University Hospital Groningen. The HIT programme aims at integration of cognitive behaviour therapy with neuroleptics, coping training, psycho-education, motivational interventions, rehabilitation, and single family treatment. In naturalistic studies the HIT programme appeared quite effective in reducing signs and symptoms in chronic therapy-refractory patients (11) as well as in first episode psychotic adolescents (12). Positive results of the HIT programme remained over time (13).

In contrast to the number of studies on effectiveness, studies on the cost-effectiveness of interventions for schizophrenia are still rare, although information on cost-effectiveness is highly relevant for policy decisions in healthcare. Only a few studies have examined costs and outcomes of some of the elements of the integrative HIT programme. One study situated in the UK (14) focused not only on the effectiveness of cognitive behaviour therapy for patients with psychosis (most patients had a diagnosis of schizophrenia), but also on the cost-effectiveness of this therapy. Results indicated that positive health outcomes were retained over a period of 18 months. Unfortunately, the economic analyses were based on incomplete information on costs of only a small number of subjects. The authors concluded that cognitive behaviour therapy could be a cost-effective intervention for this subject group. In another study (15), economic consequences of behavioural family

treatment in schizophrenia were estimated. This treatment proved to be effective, relapse rates decreased significantly, and additional costs of the intervention were compensated by decreased costs of mental health services used. Finally, the majority of currently available studies focused on the cost-effectiveness of antipsychotic medication, including the (more expensive) atypical antipsychotics, but the scope of the conducted economic evaluations in this field is narrow; cost analyses are usually restricted to direct medical costs (16-18). In sum, information on the cost-effectiveness of interventions for schizophrenia is scarce and inconclusive. One of the main shortcomings of the available economic evaluations is the limited number of included cost categories. Most studies concentrate on (often incomplete) direct medical costs without considering the inclusion of direct and indirect non-medical costs (19), like costs of informal care and productivity losses. In particular, these latter costs can be substantial in patients with schizophrenia (20, 21). However, the amount of costs depends, to some extent, on the methods used (22) to quantify these losses.
The purpose of the current paper was to describe the cost-effectiveness analysis of the HIT programme. For the assessment of the cost-effectiveness of the HIT programme, costs, inside and outside the healthcare sector, and health outcomes were compared between patients who received the HIT programme and patients who received care as usual.

Material and methods

Study design
The conducted cost-effectiveness analysis was an integral part of a study on the effectiveness of the HIT programme. Detailed information on the HIT programme, the design and results of the clinical study is described elsewhere (12, 13, 23). The study was designed as a randomised controlled clinical trial. Recruitment of patients took place in the northern and eastern part of the Netherlands. Patients were included if they met the following criteria: suffering from auditory hallucinations despite adequate treatment for at least two years, diagnosis (DSM-IV) within the schizophrenia spectrum, treated with at least two antipsychotic drugs during an adequate period of time, no previous treatment for auditory hallucinations with cognitive behaviour therapy, no current abuse of psychoactive drugs or alcohol and an IQ above 80. A battery of instruments was constructed to measure, among other things, symptoms and burden [Auditory Hallucination Rating Scale (AHRS); 24], psychopathology [Positive And Negative Syndrome

Scale (PANSS); 25] and social disabilities [Groningen Social Disabilities Scale (GSDS); 26]. Power analyses indicated that a sample size of 26 patients in each group would achieve 80% power to detect a 20% difference in PANSS score at the 5% significance level (mean condition 1: 30.3, mean condition 2: 37.7; sd 9.5). Randomisation was carried out by the Office for Medical Technology Assessment of the University Hospital Groningen. Patients were randomly assigned to the interventions, HIT or care as usual (CAU). CAU for patients with chronic schizophrenia in the Netherlands consists of medication monitoring, psycho-education and supportive counselling. Measurement was carried out by independent researchers and took place at the time of inclusion (T0), after 9 months (T9, the end of the treatment phase), and after 18 months (T18, the end of the follow-up period).

Patients

Between 1998 and 2000, in total 76 patients were randomised (37 in the HIT group and 39 in the CAU group). Ten patients withdrew from the study before T18 and one patient died of natural courses. For two other patients, information on costs during the treatment phase or follow-up period was missing and they were excluded from the economic analyses. Therefore, results of the cost-effectiveness analyses are based on the information of the remaining 63 patients (83% of the originally included patients), 31 in the HIT group and 32 in the CAU group. Relevant characteristics of the 13 patients who were excluded did not differ significantly from the other patients at the time of inclusion.

Design of the cost-effectiveness analysis

Cost-effectiveness analysis is a form of full economic evaluation, in which costs and consequences of a health programme or treatment and at least one alternative are calculated and presented in a ratio of incremental costs to incremental effects (19, 27). In the present study, costs and outcomes of patients who received the HIT programme were compared with those of patients in the CAU group. Main outcome measure of the cost-effectiveness analysis was the aggregated score on the PANSS (25). The PANSS is a 30-item, semi-structured interview with the patient on psychiatric symptoms (including hallucinations). Lower scores on the PANSS reflect better functioning. The costs per point improvement on the PANSS were expressed by means of the incremental cost-effectiveness ratio (ICER):

$$\text{ICER} = \frac{(C_{HIT} - C_{CAU})}{(P_{HIT} - P_{CAU})}$$

where C_{HIT} = mean costs per patient in the HIT group, C_{CAU} = mean costs per patient in the CAU group, P_{HIT} = mean PANSS difference score in the HIT group, P_{CAU} = mean PANSS difference score in the CAU group.

The cost-effectiveness analysis was conducted on an intention-to-treat basis, i.e. all relevant costs and effects of patients were assigned to the intervention to which they were randomised. Costs and outcomes were registered prospectively during a period of 18 months.

Assessment of costs and unit prices

The cost analyses included all cost types that were expected to differ between groups. As the study was performed from a societal perspective, the analyses did not only focus on direct medical costs, but also assessed direct and indirect non-medical costs. Table 1 shows the various cost categories and types of costs that were included in the analyses.

Table 1. Included cost categories and types of costs

Direct medical costs	Direct non-medical costs	Indirect non-medical costs
Cognitive therapy	Travel costs	Productivity losses paid labour
Inpatient care	Invested time	
Sheltered accommodation/day care	Informal care	
Outpatient and community care	Out-of-pocket costs	
General healthcare services		
Day activity institutions		
Medication		

Costs of cognitive therapy, travelling and invested time only applied to the treatment phase of the HIT programme. Costs of travelling and invested time were expenditures of patients who attended cognitive therapy sessions of the HIT programme, which was provided at a few locations in the study area. In the current study, informal care consisted mainly of invested time by relatives and acquaintances in assisting the patient. Additional costs related to the illness, like costs of damage caused by the patient, are entitled as out-of-pocket costs. The friction cost method (28, 29) was used to estimate the costs of productivity losses caused by illness-related absences from work. Under this method, production losses are assumed to be confined to the period needed to replace the sick worker: the friction period. In this study, the values used for lost productivity are estimated by the duration of absence and the net income of the patient during this period. Quantities of used resources were registered prospectively, i.e. within the context

of the current study, for all patients included in the analyses. The information was primarily collected by means of a questionnaire developed for the purpose of the current study. This questionnaire focused on various types of costs during T0-T9 and T9-T18 and assessed, among others, the number of admissions to psychiatric hospitals, the number of days patients stayed in sheltered accommodations, the number of visits to a psychiatrist or psychologist, and the number of sick leave days of patients with paid labour. Additional information, for instance medication use and the number of cognitive therapy sessions in the HIT group, was registered by various healthcare professionals involved.
Unit prices, the price of one unit of each included cost type (available on request), were mainly based on Dutch standard prices (30) in order to facilitate comparability with previous and future cost-effectiveness studies. However, for various cost types standard prices were not available and true costs of used resources were estimated. Finally, for the unit price of crisis interventions the available tariff for regular crisis intervention during the daytime was applied. All unit prices are based on the price level of the Dutch guilder in the year 2000. Results will be presented in US dollars (1 dollar = 2.19 guilder; rate of exchange at January 2000).

Discounting and sensitivity analyses
Costs and outcomes that occur after 1 year are usually discounted in cost-effectiveness analyses, because people are assumed to prefer immediate over postponed consumption (27). Most of the costs during the follow-up period (9 months after inclusion up until 18 months after inclusion) occurred in the second year. For the sake of simplicity, it was assumed that all costs during the follow-up period took place in the second year and were, therefore, eligible for discounting. The same assumptions were also applied to the health outcomes during the follow-up period. Following the recommendations of the Dutch guidelines for studies on costs (30), a discount rate of 4% was used for costs and health outcomes. Both univariate and multivariate sensitivity analyses were planned in order to provide information on the robustness of the results of the economic analyses. Only cost variables that contributed considerably to the total amount of costs (at least 10%) were included in these analyses. Additional sensitivity analyses focused on the influence of varying discount rates. Finally, the bootstrap method (31) was used to nonparametrically estimate the 95% confidence interval of calculated costs. By using this method, a large number of simulated patient populations (in this study 1000) can be created by randomly selecting patients (with replacement) from the original patient population.

Statistical analyses

All analyses were carried out using SPSS for Windows (version 10.0.7). Cost differences between groups were mainly analysed using the Mann-Whitney U test for independent samples since the vast majority of cost variables was skewly distributed. Normally distributed variables were tested with Student's t-test for independent samples. All significance test results involved two-tailed probabilities with alpha set at 0.05. Cost differences were presented descriptively when the number of patients utilising a certain cost type was (in at least one of the groups) smaller than three (32).

Results

Patients

Details of patients included in the economic analyses are briefly described in Table 2. At the time of inclusion, the mean age of patients in the HIT and CAU group was 36 and 35 years, respectively.

Table 2. Characteristics of patients included in the economic analyses

	HIT group (n=31)	CAU group (n=32)	Significance
Age			
Mean age in years (sd)	36.3 (11.1)	35.3 (10.6)	n.s. [1]
Gender			
Male	55%	53%	n.s. [2]
Diagnoses			
Paranoid schizophrenia	77%	81%	
Schizo-affective disorder	13%	16%	n.s. [2]
Psychosis NOS	10%	3%	
Hallucinations			
Duration (years) of hallucinations (sd)	13.2 (11.5)	10.3 (7.7)	n.s. [1]

[1] Student's t-test, [2] Chi-square

The number of males and females did hardly differ between groups. Most patients had diagnoses of paranoid schizophrenia. The mean duration of hallucinations was 13 years for patients in the HIT group, and 10 years for patients in the CAU group. There were no significant differences between treatment groups on any of these characteristics, nor were there any differences between groups in healthcare service use during a period of 9 months prior to the study.

Costs during the study period

Information on direct medical costs and service utilisation during the study period is presented in Table 3.

Table 3. Direct medical costs during study period (T0-T18)

Healthcare services and cost types	Costs ($) of HIT group (n=31)				Costs ($) of CAU group (n=32)				Sign. of difference[2]
	mean	sd	median	n'[1]	mean	sd	median	n'[1]	
HIT programme									
Cognitive therapy	1059	536	1054	31	-	-	-	-	-
Training[3]	177	-	-	31	-	-	-	-	-
Supervision[3]	381	-	-	31	-	-	-	-	-
(Semi-)inpatient care									
Psychiatric hospital admission	23550	18417	22117	4	5817	12859	623	6	n.s.
Sheltered accommodation	33096	11618	34415	9	35232	8763	39054	13	n.s.
Day care	1776	179	1776	2	2284	1436	2284	2	-[4]
Outpatient/community care									
Psychiatrist	207	212	114	20	281	345	143	29	p<.02
Psychologist	531	231	531	5	352	321	314	5	n.s.
Social-psychiatric nurse	267	261	226	13	476	269	415	16	n.s.
Social worker	72	51	50	5	88	103	88	2	-[4]
Crisis intervention	130	0	130	2	187	88	187	2	-[4]
Psychiatric home care	440	508	221	6	2329	3274	723	12	n.s.
Other outpatient care	227	-	227	1	892	838	790	4	-[4]
CAD [5]	-	-	-	0	-	-	-	0	-[4]
General healthcare									
General practitioner	138	188	74	9	64	80	34	13	n.s.
Alternative healthcare	94	66	84	3	45	26	49	3	n.s.
Emergency care	-	-	-	0	-	-	-	0	-[4]
Other general healthcare	-	-	-	0	379	-	379	1	-[4]
Day activity institutions									
Day activity centre	1700	1574	1756	7	1400	1545	1322	15	n.s.
Drop-in centre	1492	2509	61	3	964	1300	232	11	p<.02
Other day activity institutions	858	770	1055	3	712	963	317	5	n.s.
Medication									
Prescribed medication	1807	1500	1585	31	2255	1750	1810	32	n.s.
Non-prescribed medication	62	-	62	1	139	154	139	2	-[4]

[1] n' represents the number of patients using the health services and cost types concerned. Mean and median values are based on these patients.
[2] All patients of both groups were included in these analyses as long as there was no missing patient data on the variable involved.
[3] Constant value, calculated for the current number of included patients.
[4] Not tested due to small number of patients using this service.
[5] CAD = Consultation Office for Alcohol and Drug Addiction.

The HIT programme was provided during the first 9 months of the study and the associated costs (i.e. costs of therapy, training and supervision presented in Table 3, but also travel and time costs of patients presented in Table 4) did not apply to patients in the CAU group. Total costs of the HIT programme were $52,646 (mean costs per patient were $1,698) and constituted 9% of the total costs of patients in the HIT group. Significant differences in favour of patients in the HIT group were found for a few cost types; costs associated with consulting psychiatrists, and costs of visiting drop-in centres (non-intensive social support).
Table 4 displays the direct and indirect non-medical costs of both groups during the study period. No significant differences between groups were found for these cost types. Mean total costs per patient (sum of all costs in Table 3 en 4) in the HIT group during the entire study period were $18,237 (median costs $6,840). For patients in the CAU group, mean total costs per patient were $21,436 (median costs $12,677). Note that the total costs were substantially influenced by the costs of sheltered accommodations and admissions to psychiatric hospitals. Differences between the total costs of both treatments were not statistically significant.

Table 4. Direct en indirect non-medical costs (T0-T18)

Services and cost types	Costs ($) of HIT group (n=31)				Costs ($) of CAU group (n=32)				Sign. of diffe-rence[2]
	mean	sd	median	n'[1]	mean	sd	median	n'[1]	
Travel costs	135	171	84	14	-	-	-	-	-
Time costs	137	66	130	5	-	-	-	-	-
Informal care	1420	1167	1245	11	1876	1300	1739	14	n.s.
Out-of-pocket costs	351	434	351	2	-	-	-	0	-[3]
Productivity losses	2095	1234	1973	5	1834	1129	1834	2	-[3]

[1] n' represents the number of patients using the services and cost types concerned. Mean and median values are based on these patients.
[2] All patients of both groups were included in these analyses as long as there was no missing patient data on the variable involved. Costs were $0,- for patients who did not use the service concerned.
[3] Not tested due to small number of patients using this cost type.

PANSS results

Results of the PANSS, the main outcome measure in the cost-effectiveness analysis, are listed in Table 5. Note that lower scores on the PANSS reflect better functioning. Results of T0 and T18 were relevant for the calculation of the incremental cost-effectiveness ratio (ICER). Difference scores were computed by subtracting the discounted T18 score from the results of T0. Although these difference scores were in favour of the HIT group, differences did not approach a statistically significant level.

Table 5. PANSS results [1]

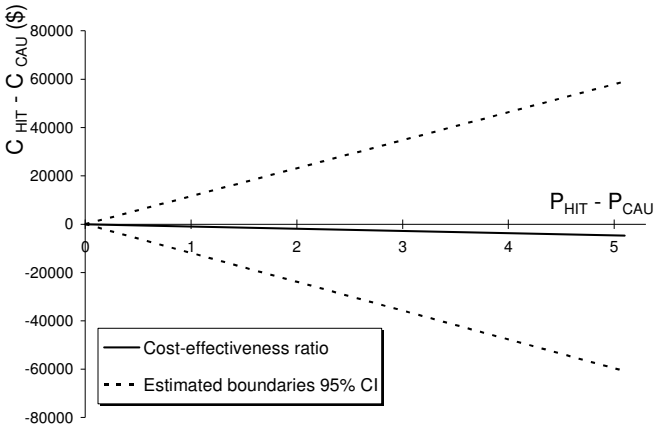
PANSS scores	HIT group (n=31)	CAU group (n=32)	Significance of difference
PANSS T0	57.1	60.2	n.s.
PANSS T9	51.0	61.7	p<.01
PANSS T18	51.1	57.3	n.s.

[1] = Listed PANSS scores are mean values.

Cost-effectiveness analysis

There were no significant differences between groups in changes in PANSS scores by T18, nor in total costs over the study period. Thus, there is no clear cost-effectiveness advantage of one condition over another. However, the trend toward lower mean costs and an improvement in PANSS scores for the HIT group suggested that calculation of an ICER would be informative. In order to enable generalisation of the current results to future situations, it was decided to assess the ICER in combination with the accompanying 95% confidence interval. For the cost component of the cost-effectiveness analysis, mean costs per patient during the study period were used. As an improvement in functioning is reflected by a decrease in the PANSS score, it was decided to multiply the calculated PANSS difference scores by –1. In this way, improved functioning is expressed in a positive difference score, which simplifies the interpretation of the ICER.

Figure 1. Cost-effectiveness ratio and estimated 95% confidence interval



The calculated value of the ICER, using the formula described in the method section, was – 936. This negative value indicates that patients in the HIT group generated fewer costs and had better results on the PANSS. The estimated 95% confidence interval is graphically presented along with the calculated ICER in Figure 1. As negative ICERs may cause some inaccuracies with regard to the estimation of confidence intervals (33), the presented boundaries should be considered as approximations.

Sensitivity analyses

For the uni- and multivariate sensitivity analyses, cost variables that covered at least 10% of total costs per patient group were identified. In the univariate analyses, identified cost types per group were increased and decreased one at a time by 20% and differences in total costs were subsequently tested. However, no significant differences were found. In the multivariate analyses, all identified cost types of one group were increased while the identified cost types of the other group were decreased by 20%. Significant differences ($p<.03$) were found when identified costs of the HIT group were decreased and identified costs of the CAU group were increased. Variations of the discount rate (3% and 5% instead of 4%) only had minor consequences for the results of the analyses.

In order to provide additional information for the interpretation of the results of the economic analyses, the bootstrap method was used to determine the range of future differences in costs (incremental costs) associated with the HIT programme and CAU. The median cost difference between both interventions calculated with the bootstrap method was - $3,413. The lower and upper boundaries of the accompanying 95% confidence interval were - $12,050 and + $6,637, respectively. Again, negative values indicate fewer generated costs for patients in the HIT group.

Discussion

This paper presented the cost-effectiveness analysis of the HIT programme, an integrated treatment for persistent auditory hallucinations in patients with schizophrenia. In the cost-effectiveness analysis, a comparison was made between costs and outcomes of patients who received either the HIT programme or CAU.
The assessment of healthcare utilisation and associated costs was an essential part of the economic analyses. Results indicated that the total amount of generated costs of both patient groups was influenced substantially by the costs of sheltered accommodations and admissions to psychiatric hospitals. These results are in accordance with previous studies on service utilisation and costs of patients with chronic schizophrenia (1, 34, 35). Costs of medication (about 10% of total costs) were somewhat higher in the present study compared with other studies (2). It is most likely that these higher medication costs were at least partly due to increasing use of expensive atypical antipsychotics in recent years. Furthermore, results of the cost analyses indicated that the mean costs of the HIT programme per patient were $1,698 during a treatment phase of nine months. These costs constituted 9% of the total costs of patients in the HIT group.
As the cost-effectiveness analysis was performed from a societal perspective, costs outside the healthcare sector were also included in the analyses. The total amount of non-medical costs was highly influenced by costs related to informal care (71% of total non-medical costs). In the present study, costs associated with productivity losses only had a minor influence on the total amount of non-medical costs. This finding is in contrast with some other studies (20, 21) where productivity costs constituted a substantial part of total costs, which is mainly due to the methods used to quantify productivity losses (22).
The absence of statistically significant differences in total costs seems to be the result of the skewed distribution of cost variables in combination with the size of the study population. This problem is quite common in economic analyses (14, 36). Fortunately, there are several methods that can (partially) deal with the uncertainties surrounding skewly distributed costs. In the present study the bootstrap method was used (31). This method provided additional information on the skewly distributed costs by nonparametrically determining the 95% confidence interval. Results indicated that future cost differences will, in most cases, be in favour of the HIT programme.
Cost-effectiveness analyses require the selection of a primary outcome measure. In the present study the PANSS was chosen for this purpose and power analyses were based on this instrument. Although differences between groups in total PANSS score were statistically significant at T9 and in favour of the HIT group, patients in

the CAU group improved considerably during the follow-up period, which led to a smaller and non-significant difference (still in favour of the HIT group) at T18. As a consequence, calculated difference scores for the entire study period (T18-T0) were in favour of the HIT programme, but did not demonstrate statistically significant differences between groups.
Additional evidence for the superiority of the HIT programme was found through the administered questionnaires on symptoms (AHRS), quality of life (WHOQoL-BREF: 37) and social functioning (GSDS). Results indicated that patients in the HIT group had more control over voices, experienced less subjective distress, and demonstrated less social disabilities than patients in the CAU condition (personal communication).
In conclusion, a simple comparison of costs and outcomes indicates that there is no significant cost-effectiveness advantage of the HIT programme over CAU. Additional analyses demonstrated that future application of the HIT programme will, in most cases, lead to a reduction of societal costs associated with chronic schizophrenia. At the present time, only a small number of studies has focused on the cost-effectiveness of interventions for patients with schizophrenia. As societal costs of schizophrenia are high and policy decisions in healthcare are increasingly based on information concerning costs and outcomes, it is to be expected that the number of cost-effectiveness analyses in this field of expertise will expand considerably in the following years, which may add to the interpretation of the results of the present study as well.

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Chapter 3

Cost-effectiveness of Cognitive Self-Therapy in patients with depression and anxiety disorders

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Submitted

Abstract

Introduction: Self-therapy interventions could potentially reduce expenses and the need for care in the treatment of depression and anxiety disorders. The current study assessed the cost-effectiveness of Cognitive Self-Therapy (CST) in patients with depression and anxiety disorders.
Method: 151 patients were randomly assigned to CST or treatment as usual (TAU), and prospectively followed during 18 months. The Symptom Checklist 90 (SCL-90) was the primary outcome measure in the cost-effectiveness analysis.
Results: Mean costs of patients in the CST group (€4028) were lower than the mean costs of patients who received TAU (€4837). Results of the SCL-90 were slightly in favour of CST. Additional analyses indicated that CST dominated TAU in 50% of the bootstrap replications.
Conclusion: Differences in health outcomes between CST and TAU were modest. Mean costs of patients in the CST group were €809 lower than in TAU. Valuing an additional unit of health outcome at €100 will lead to an 83% probability that CST is cost-effective.

Introduction

Many patients suffering from depression or anxiety disorders can not adequately be treated within current European healthcare systems (1). The number of available therapists is limited and unable to meet the extensive need for care. Unfortunately, the consequences of inadequate treatment of mental illness can be serious, both for the well-being of patients as for national healthcare expenses, especially in case of recurring or chronic mental disorders (2, 3).
Various studies have indicated that self-help strategies can form an effective alternative for treatment provided by therapists, also in patients with depression or anxiety disorders (4). Self-help strategies are currently provided to patients in various formats, including self-help manuals and computerised programmes. For policy makers, the potential cost savings associated with self-help strategies are particularly interesting. However, only a limited number of studies analysed both costs and health outcomes of self-help strategies aimed at emotional disorders, and the methodological quality of available studies has been questioned (5). In one of the rare economic evaluations of self-help strategies in patients with depression and anxiety disorders (6), the cost-effectiveness of computerised cognitive behavioural therapy (CBT) was examined. Based on costs and health outcomes registered during 8 months, the authors concluded that computerised CBT was likely to be cost-effective compared to treatment as usual. These findings underline the relevance of economic evaluations of self-help strategies in mental healthcare, and provide support for economic studies on other forms of self-help strategies as well.
Recently, a randomised clinical trial (7) focused on Cognitive Self-Therapy (CST) in patients with depression and anxiety disorders. CST integrates self-help manuals and depression courses with support provided by paraprofessionals. There were prior indications of the effectiveness of CST (based on an unpublished pilot study), but no large trials had been conducted before.

Aims of the study
This paper will present the results of the economic evaluation that was performed alongside the clinical trial on CST. The economic evaluation assessed the cost-effectiveness of CST in comparison with treatment as usual (TAU) in patients with depression and anxiety disorders.

Material and Methods

The economic evaluation was part of an 18-month clinical study on the effectiveness of CST in patients with depression and anxiety disorders. Details on the design and results of the clinical study are provided elsewhere (7).

Study population

Recruitment of patients took place between 2000 and 2002 in four outpatient centres located in different parts of the Netherlands. Patients were eligible for the study if they had a diagnosis of depression or generalised anxiety disorder. Additional selection criteria included a history of mental healthcare utilisation of at least two years, aged between 18 and 65, and an awareness of personal vulnerability in social contacts and/or relationships. Patients were excluded if they displayed suicidal behaviour or psychotic symptoms, had a comorbid diagnosis within the autistic spectrum or an organic disorder, were drug or alcohol dependent, or mentally handicapped (IQ<85).

Randomisation procedure and interventions

Stratified randomisation was applied to ensure the comparability of patient groups. Strata were based on age; <40 years of age or >=40 years of age, and duration of complaints; <7 years or >= 7 years. Patients were randomly assigned to two intervention arms, CST or treatment as usual (TAU). Both interventions were provided in outpatient centres and included a first contact for diagnostic purposes. During the study, patients received any form of regular care they required in addition to the care that was part of the interventions.

TAU in the Netherlands consisted of 10-20 contacts with a psychologist, psychiatric nurse or social worker. During these contacts, healthcare professionals mainly focused on problem solving and coping strategies, but they did not follow a prescribed treatment protocol.

CST is a method developed to restructure cognitive schemata and address problems in social functioning and relationships. Psychiatric nurses, social workers and psychologists can be trained to perform CST programmes and to teach the CST method to patients. Patients use a CST manual (8) that acquaints them with the treatment principles. The patients' role in the treatment gradually evolves into that of a "paraprofessional", such that they finally conduct CST sessions in reciprocal relationships with peers. The CST programme consists of: a) Preparatory phase of one to three 45 minute meetings, for informing the patient and for checking whether the patient is able and willing to participate in the CST course; b) Orientation course of three mornings, once a week, during which the patients

practice with peers, before definitely making the choice to continue with the next phase; c) Basic course of 5 days, once a week, in which patients learn to manage a CST session. Those who perform a CST session adequately with peers will become certified to participate in the last phase of the CST programme: d) Self-Therapy meetings, once a week, led by peers in accordance with the manual as was taught during the basic course. All certified patients had the free choice of participating in Self-Therapy meetings whenever they liked and could attend these meetings during the study period. Before the beginning of the study, the CST programme was uniformly implemented in all participating centres.

Outcome measures and power analysis

The Symptom Checklist 90 (SCL-90; 9) was the main outcome measure of the study. The SCL-90 is a multi-dimensional self-report inventory that can identify psychological problems and symptoms of psychopathology. The total score of the SCL-90 is based on nine subscales and can range from 90 – 450, where lower scores indicate better functioning. Power analyses were based on characteristics of this instrument in the patient population under study; 61 patients were required in each treatment condition in order to detect a clinically relevant difference of 23 points between groups (SD=50) with an alpha of .05 and a power of 80%. In total 151 patients were included in the study to account for an estimated drop-out rate of 20%. Measurement took place at six-month intervals, starting at the time of inclusion until the end of the follow-up period 18 months later (T0, T6, T12, T18).
Various additional instruments were administered during the clinical study, focusing on depressive symptoms (Beck Depression Inventory; 10), social anxiety (State-Trait Anxiety Inventory; 11), social functioning (Groningen Social Disabilities Schedule; 12) and quality of life (World Health Organization Quality of Life Assessment-BREF; 13). Results of these additional instruments could not directly be included in the economic evaluation due to the theoretical framework of cost-effectiveness analysis, which requires the inclusion of a single outcome.

Costs and unit prices

The economic evaluation was conducted from a societal perspective, therefore costs were assessed both within and outside the healthcare sector. Table 1 shows the various types of costs that were registered during the 18 months of the study. Costs of CST included costs of therapists who were training, educating and supporting patients during the various stages of the CST programme. Costs of travelling and invested time related to the CST meetings were registered during the study. Costs of invested time were valued in monetary terms based on the net income of patients.

Table 1. Registered medical and non-medical costs

Direct medical costs	Direct non-medical costs	Indirect non-medical costs
Cognitive Self-Therapy (CST)	Travel costs	Productivity losses with and without absence from work
Inpatient and semi-inpatient care	Time costs	
Outpatient and community care	Informal care	
General healthcare	Out-of-pocket costs	
Day activity institutions		
Medication		

Costs of informal care were based on the monetary valuation of the time invested by relatives or acquaintances in helping or assisting the patient. Additional costs related to the illness, like costs of non-prescribed medication, are combined under the heading out-of-pocket costs. The friction cost method (14, 15) was applied for estimating costs associated with productivity losses. When applying the friction cost method, production losses are assumed to be confined to the period needed to replace the sick worker (currently estimated at five months in the Netherlands). Quantities of used resources were registered for all the patients available at the various times of measurement. The information on costs was primarily collected by means of a questionnaire previously used in economic evaluations in mental healthcare (16). This questionnaire assessed, among others, number of admissions to psychiatric hospitals, contacts with psychiatrists and psychologists, and sick leave days of patients. Additional information, like medication use, was collected through various healthcare professionals. In order to facilitate comparisons with other economic evaluations, unit prices, i.e. the price of one unit of each included cost type (available on request), were mainly based on Dutch standard prices (17). True costs of used resources were estimated when standard prices were not available. All unit prices were based on the price level of the Euro in the year 2003. Reference prices established for previous years were adjusted to prices of 2003 by applying the consumer price index.

Cost-effectiveness analysis

In cost-effectiveness analysis, costs and the primary health outcome associated with an intervention are used to calculate the incremental cost-effectiveness ratio relative to one or more alternatives (18). In the present study, costs and health outcomes of patients who received CST were compared with those of patients in the TAU condition. Primary outcome measure in the cost-effectiveness analysis was the SCL-90, the instrument on which power analyses of the clinical study were

based. Costs per point improvement on the SCL-90 were expressed by the incremental cost-effectiveness ratio (ICER):

$$ICER = \frac{(C_{CST} - C_{TAU})}{(SCL90_{CST} - SCL90_{TAU})}$$

Where C_{CST} = mean costs per patient in the CST group, C_{TAU} = mean costs per patient in the TAU group, $SCL90_{CST}$ = mean SCL-90 difference score in the CST group, $SCL90_{TAU}$ = mean SCL-90 difference score in the TAU group.

In the standard analyses costs and health outcomes were not discounted. Discounting would have had a minor influence on differences between groups in the present study of 18 months (discounting will be addressed in the sensitivity analyses). Uncertainty surrounding the calculated ICER was examined by the bootstrap method (19). Bootstrapping is an iterative method that consists of randomly selecting patient data (with replacement) from the observed population to create a simulated distribution of data. ICERs were calculated for each of the bootstrap iterations (5000 in the present study), simulated values of the mean estimates for the cost and outcome differences were added to the cost-effectiveness plane (20). Finally, cost-effectiveness acceptability curves (CEACs) (21, 22) were calculated. CEACs inform decision-makers on the probability that an intervention will be cost-effective for increasing monetary values placed on an additional unit of health outcome.

Sensitivity analysis

Various sensitivity analyses were performed in order to provide information on the robustness of the results of the economic evaluation. Discount rates were varied (4% and 5% instead of 0%) and consequences for differences between groups were examined. Costs of hospital admissions are known to have a large impact on total costs in mental healthcare. In order to examine the uncertainty of this cost aspect in the current study, costs of hospital admissions were increased with 20% in one of the intervention arms, while at the same time being decreased with 20% in the other. Subsequently, consequences for differences in total costs between groups were analysed. Additional sensitivity analyses focused on the exclusion of costs related to productivity losses.

Statistical analysis

Analyses of costs and clinical outcomes were conducted on an 'intention-to-treat' basis, using mixed models under the assumption of missingness at random. Mixed models is a repeated measurement analysis that uses all available data, i.e. also of patients for whom one or more measurements are missing. The applied models included main effects of treatment condition and assessment time and their interaction, with a random effect of subject. The baseline score of the SCL-90 was included to account for initial differences between groups.

Between-group baseline characteristics were analysed with Student's T-tests for continuous variables and Pearson chi-square tests for categorical variables. P-values less than 0.05 were considered statistically significant. All the analyses were carried out with SPSS 12.0.2 for Windows (SPSS, Inc, Illinois, USA).

Results

Patient characteristics at baseline

The CST group consisted of 52 women (69%) and 23 men (31%) with a mean age of 40.7 years (SD=8.9). In the TAU group there were 48 women (63%) and 28 men (37%) with a mean age of 41.9 years (SD=9.1). Main diagnoses in both groups were depressive disorder (91% in CST, 97% in TAU) and generalised anxiety disorder (9% in CST, 3% in TAU). More than half of the patients (52%) had a co-morbid diagnosis of a depressive or anxiety disorder. The number of years since first contact with mental healthcare was 12.2 years (SD = 7.6) in the CST group and 13.1 years (SD = 9.0) in the TAU group. There were no statistically significant differences between groups on demographic (gender, age, living situation, level of education) or clinical characteristics (primary diagnosis, co-morbidity, time of first psychiatric contact, family psychiatric history) at baseline.

Service use and costs

Table 2 shows information on medical and non-medical cost, as well as service use. Means of each cost type are based on all patients in both groups. If a patient did not make use of a specific cost type, costs of €0 were applied when calculating group means. In addition, mean costs and number of patients who actually used the health services are presented as well.

Table 2. Medical and non-medical costs (€) during T0-T18

Healthcare services and cost types	CST group (n=61)		TAU group (n=59)	
	Mean costs whole group (SD)	Mean costs[1] (N)	Mean costs whole group (SD)	Mean costs[1] (N)
CST				
Therapy/training	323 (245)	352 (56)	-	-
In-patient/semi-inpatient care				
Psychiatric hospital admission	671 (3717)	20474 (2)	1546 (7445)	18247 (5)
Day care	1 (11)	88 (1)	84 (353)	1236 (4)
Outpatient/community care				
Psychiatrist	70 (129)	157 (27)	82 (139)	194 (25)
Psychologist	143 (212)	265 (33)	186 (324)	422 (26)
Social psychiatric nurse	57 (117)	175 (20)	134 (240)	343 (23)
Social worker	22 (73)	133 (10)	56 (134)	220 (15)
Crisis intervention	2 (18)	139 (1)	5 (25)	139 (2)
Psychiatric home care	9 (67)	523 (1)	33 (253)	1944 (1)
CAD[2]	0 (-)	0 (0)	0 (-)	0 (0)
Other out-patient care	249 (641)	893 (17)	813 (995)	1263 (38)
General healthcare				
General practitioner	76 (182)	111 (42)	44 (97)	89 (29)
Alternative healthcare	22 (68)	190 (7)	27 (123)	319 (5)
Home care	3 (13)	51 (3)	3 (13)	46 (4)
Emergency care	0 (-)	0 (0)	0 (-)	0 (0)
Other general healthcare	23 (109)	205 (7)	18 (68)	155 (7)
Day activity institutions				
Day activity center	29 (171)	894 (2)	0 (-)	0 (0)
Other institutions	0 (-)	0 (0)	0 (-)	0 (0)
Medication				
Prescribed medication	256 (312)	363 (43)	437 (467)	537 (48)
Various non-medical costs				
Travel costs	17 (24)	25 (42)	-	-
Time costs	420 (403)	458 (56)	-	-
Informal care	16 (40)	97 (10)	7 (22)	53 (8)
Out-of-pocket costs	53 (157)	248 (13)	42 (136)	191 (13)
Productivity losses				
Paid work	1335 (2849)	4073 (20)	935 (1721)	2509 (22)
Paid work without absence	229 (1613)	4662 (3)	384 (1691)	2519 (9)

[1] Mean costs of persons using the health services and cost types involved (number of patients using these services between brackets).
[2] Consultation Office for Alcohol and Drug Addiction.

Total costs (medical and non-medical) of providing the CST intervention were estimated at €760 per patient. These costs consisted of costs of teaching CST to patients (€323), as well as travel and time costs of patients directly related to the

CST meetings (€437). Costs of psychiatric hospital admissions, medication use and 'other out-patient care' contributed substantially to total medical costs in both groups. 'Other out-patient care' consisted of various types of treatment, including group therapy and social skills training. Travel costs and costs of invested time were only assessed when directly related to the CST intervention. Costs related to productivity losses, with and without absence from work, were relatively high in both groups.
An overview of total costs during each measurement period and total costs during the 18 months of the study is presented in Table 3.

Table 3. Total costs (€) during the study

Measurement	CST group			TAU group			95% CI[1]
	n	Mean	Median	n	Mean	Median	
T0-T6	72	1897	1102	70	1970	847	-1278, +1016
T6-T12	65	809	543	62	1428	735	-1357, -33
T12-T18	63	1121	356	61	1680	411	-2472, +961
T0-T18[2]	61	4028	2255	59	4837	2511	-3693, +1460

[1] 95% confidence interval of the mean cost differences between groups per measurement, generated by the bootstrap method. Lower and upper boundaries are presented.
[2] Displayed mean total costs during T0-T18 are based on data of patients for whom all the relevant measurements were available (complete cases).

The costs of teaching CST to patients in the CST condition were generated during T0-T6, while the costs of attending peer meetings mainly took place during the following periods. During T6-T12, mean total costs in the CST group were lower, partially related to a decreased use of healthcare services. In the last six months of the study, total costs slowly increased again for patients in the CST group. For patients in the TAU group, there was somewhat less variation in total costs during the study.
Mean total costs during the entire study period were €4028 per patient in the CST group (median costs €2255) and €4837 per patient in the TAU group (median costs €2511). Differences in mean total costs per measurement between groups were examined by 95% confidence intervals (CI) generated by the bootstrap method, in addition to the longitudinal analyses with mixed models. Differences in mean total costs during the 18 months of the study were not statistically significant (95% CI lower boundary: -€3693; upper boundary: +€1460) for patients for whom all the measurements were available. Results of the mixed model analyses on costs during T0-T18 are displayed in Table 4.

Table 4. ANOVA table based on mixed effect analyses of costs and SCL-90 results

Outcome measure with model effects	df	F	p
Costs			
Effects			
Intervention	(1,138)	0.04	0.85
Time	(2,258)	32.14	<.001
Intervention * Time	(2,258)	0.63	0.53
SCL-90			
Effects			
Intervention	(1,148)	0.57	0.45
Time	(3,379)	31.50	<.001
Intervention * Time	(3,379)	0.13	0.90

Mixed effect analyses included a random effect of subject. Differences at baseline were corrected by means of covariance adjustment for SCL-90 results.

In the mixed model analyses, a significant effect of time was found; i.e. differences were found between costs over time for both groups. However, there was no significant treatment effect, nor was there a significant effect of the interaction between treatment and time. The fact that no significant differences between groups were found for costs should be interpreted with some caution, since the study was powered (as most economic evaluations) to demonstrate differences in health outcomes and not costs.

Primary health outcome

Results of the SCL-90, the primary health outcome measure, are displayed in Table 5. In the mixed model analyses (Table 4), baseline SCL-90 scores were included as covariate due to the initial differences on this outcome measure between groups.

Table 5. Results of the SCL-90*, means and standard deviations

Measurement	CST group		TAU group	
	n	Mean (SD)	n	Mean (SD)
T0	75	217.5 (54.2)	76	238.8 (58.6)
T6	70	184.7 (60.4)	71	211.0 (70.9)
T12	64	182.9 (68.8)	59	201.2 (79.7)
T18	62	178.5 (66.9)	59	200.3 (75.6)

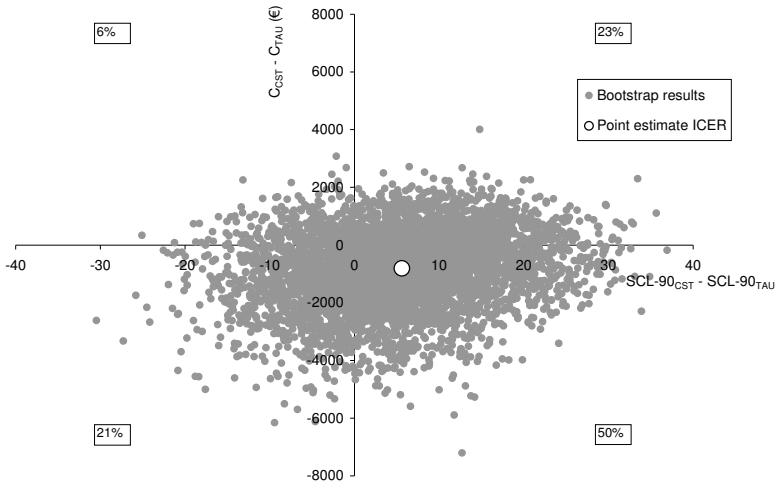
* Lower scores indicate better functioning.

The effect of time was significant (later assessments showed lower scores in both groups), but there was no significant difference between treatments, nor a significant effect of the interaction between treatment and time.

Cost-effectiveness analysis

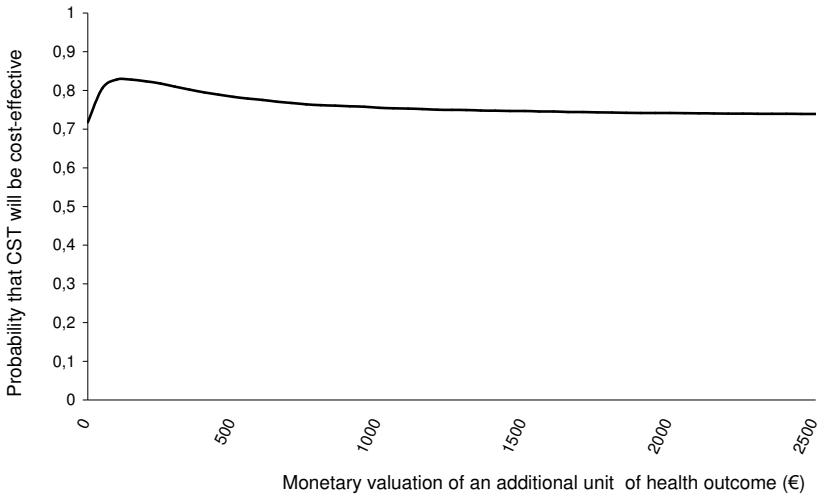
The point estimate of the ICER and the results of the bootstrap analyses are presented in the cost-effectiveness plane (CEP) in Figure 1. The calculated value of the ICER was –€144 per point improvement on the SCL-90. Here, the negative value indicates that CST was associated with lower mean costs and better health outcomes. For each quadrant of the CEP, information is provided on the percentage of bootstrap simulations located in that quadrant.

Figure 1. Results of the cost-effectiveness analysis and bootstrap method



Approximately 50% of the estimated mean cost and effect differences is located in the southeast quadrant. In other words, CST dominates TAU in 50% of the cases. Interpretation of outcomes in the northeast and southwest quadrants depends on how much decision-makers are willing to pay for an additional unit of health outcome. Figure 2 shows the probability that CST will be cost-effective for increasing monetary values placed on an additional unit of health outcome. When decision-makers are willing to pay €100 per point improvement on the SCL-90, the probability that CST will be cost-effective increases up to 83%, and subsequently decreases. This decrease is due to the location of the joint density in the north-east and south-west quadrants of the cost-effectiveness plane (21).

Figure 2. Cost-effectiveness acceptability curve



Sensitivity analyses

In the first type of sensitivity analysis, discount rates were varied and consequences for differences in mean total costs between groups were studied. Costs were discounted at 4% and 5%, instead of 0% in the standard analyses. Differences in mean total costs between groups were slightly smaller, i.e. €787 (4%) and €781 (5%) instead of €809 (0%) in favour of CST in the standard analyses. Other sensitivity analyses focused on variations in costs of hospital admissions, a cost category that may contribute considerably to the total amount of costs in mental healthcare (24% of total costs in current study). First, these costs were increased with 20% in the CST group, while at the same time being decreased with 20% in the TAU group. Subsequently, hospital costs were decreased by 20% in CST and increased in the TAU condition. The consequences of these variations for differences in mean total costs between groups were examined. Confidence intervals estimated by the bootstrap method indicated that mean cost differences between groups (€366 and €1253 in favour of CST, respectively) were not significant. Additional sensitivity analyses focused on productivity losses. When excluding costs of productivity losses, mean total costs were €2461 in the CST group and €3516 in the TAU group. In this alternative analysis, differences in mean total costs between groups (€1055) are more pronounced than in the standard analyses (€809).

Discussion

The current paper presented the results of the cost-effectiveness analysis that was part of an 18-month clinical study focusing on CST in patients with depression and anxiety disorders. A comparison was made between costs and health outcomes of patients who were randomly assigned to one of two treatment arms, CST or TAU. Overall results indicated that there were modest differences in health outcomes between CST and TAU. Furthermore, mean total costs of patients in the CST group were €809 lower than the costs of patients in TAU.

Cost types that contributed considerably to the total amount of costs were related to hospital admissions, medication use, and 'other out-patient care'. Furthermore, costs of productivity losses with or without absence from work were relatively high, which is in line with the results of previous studies examining (societal) costs of patients with depression or anxiety disorders (23, 24). The costs of training therapists in CST were not included in the current study. However, training costs will be relevant for decision-makers when considering the implementation of CST in current healthcare systems.

The primary outcome measure of the cost-effectiveness analysis was the SCL-90. Differences between groups on the SCL-90 were much smaller than the assumed clinically relevant difference on which power analyses during the design phase of the study were based. The various instruments administered in addition to the SCL-90 showed results comparable with the primary outcome measure (7). The overall outcomes of these instruments, which measured depressive symptoms, social anxiety, social functioning and quality of life, demonstrated that there were no statistically significant differences between groups on these aspects of health. As indicated by a recent literature overview (4), self-help strategies are commonly associated with results that seem comparable to those of other treatments. Therefore, it may be more appropriate to design studies on self-help strategies, including economic evaluations, as non-inferiority studies instead of superiority trials. Non-inferiority studies intend to show that an intervention is at least equal to an alternative in terms of effectiveness (25). Non-inferiority designs can be applied when there are other advantages to be gained from an intervention than strictly improving effectiveness compared to other interventions. For instance, when an intervention leads to a decrease in healthcare utilisation and lower related healthcare costs, as seems to be the case for self-help strategies.

Results of longitudinal studies can be biased by missing data due to patients who drop out or are lost to follow-up (26). Recently, the potential impact of missing data has also been acknowledged in the area of economic evaluation (27). In the current study, mixed models were used for longitudinal analyses of costs and

health outcomes to deal with missing data. In the mixed model analyses, baseline results of the SCL-90 were included as covariate to correct for initial differences between groups.

Cost-effectiveness acceptability curves were assessed to estimate the probability that CST will be cost-effective for increasing monetary valuations per unit of health outcome gained, which is considered to be relevant information for decision-makers. Unfortunately, there is currently no (inter)national consensus on acceptable benchmarks for an additional unit of health outcome, neither for generic outcomes as the QALY (Quality-Adjusted Life Years) nor for more specific outcomes like the SCL-90 applied in the current study. Decision-makers will therefore have to interpret whether the indicated costs per additional unit of health outcome seem to be acceptable or not.

Comparing the overall outcomes of the current cost-effectiveness analysis with other economic studies on self-help treatments is complicated because of the limited follow-up period of published studies. The time horizon of available studies typically ranges from 3 to 8 months (5, 6). Conclusions based on such short study periods should be interpreted with some caution. Especially since initial positive consequences of psychiatric interventions may diminish over time (28). In the present study, costs of patients in the CST condition slowly increased again in the last six months of the study, after a drop in service use during the previous measurement period. In order to adequately inform decision-makers, study periods of at least 12 to 18 months seem essential for economic studies in the field of mental healthcare.

While the advantages of self-help strategies seem obvious, results of available economic studies do not always unambiguously confirm its potential benefits for the healthcare system in general, or healthcare expenses in particular. In terms of health outcomes, self-help strategies generally appear to be comparable with treatment provided by therapists. Current results indicated that CST in patients with depression and anxiety disorders will reduce societal costs, and is associated with somewhat better health outcomes than TAU. Valuing an additional unit of health outcome at €100 will lead to an 83% probability that CST is cost-effective. Consequently, CST could be applied to relieve the burden of many patients with depression or anxiety disorders who currently do not receive the necessary care due to a limited number of available therapists. Future economic studies focusing on self-help strategies (for instance in patients with a first episode of depression) may profit from the suggestions made in the present paper, including the use of a non-inferiority design and a follow-up period of at least 12 to 18 months.

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Chapter 4

Cost-effectiveness of a psycho-educational prevention programme for depression in primary care

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Submitted

Abstract

Background: Major depression often runs a chronic-recurrent course with multiple episodes, is highly disabling for patients, and is associated with a considerable economic burden for society. The present study examined the cost-effectiveness of a Psycho-Educational Prevention programme (PEP) aimed at improving the long-term outcome of depression in primary care.
Methods: Patients with depression were randomly assigned to care as usual (CAU) or CAU enriched with one of three forms of PEP; PEP alone, psychiatric consultation followed by PEP (psychiatrist-enhanced PEP), and cognitive behavioural therapy followed by PEP (CBT-enhanced PEP). The economic evaluation was performed from a societal perspective, costs and health outcomes were registered during a period of 36 months. Proportion of depression-free time was used as the primary outcome measure in the cost-effectiveness analysis.
Results: Mean costs were €8200 in the CAU group, €9816 in the PEP group, €9844 in the psychiatrist-enhanced PEP group, and €9254 in the CBT-enhanced PEP group. Health outcomes in the psychiatrist-enhanced PEP and CBT-enhanced PEP groups were slightly better than in the CAU group. CBT-enhanced PEP had the most positive outcomes of the three PEP interventions, as indicated by cost-effectiveness acceptability curves.
Conclusions: The basic PEP intervention was not cost-effective in comparison with CAU. For the other variants of PEP, costs were higher but health outcomes were slightly better. If decision-makers are willing to pay up to €1500 for an additional proportion of depression-free time, the probability that CBT-enhanced PEP will be cost-effective increases to 70%. Findings of this study seem to provide little support for the implementation of PEP in current healthcare systems.

Introduction

Major depression is a prevalent mental disorder that often runs an intermittent lifelong course, with multiple relapses and recurrences, and frequently incomplete remission between episodes. It is considered to be among the most disabling illnesses (1), and both treated and untreated depression negatively affects many aspects of life (2-4). From an economic perspective, the consequences of depression are substantial as well. It has been estimated that 1-2 % of national healthcare expenses in Western countries is spent on the treatment of depressive disorders (5, 6). Important factors contributing to the considerable costs associated with depression are the high prevalence, early age of onset, and large risk of relapse and recurrence. Moreover, for many patients depression becomes a chronic condition, leading to an extensive use of healthcare resources in subsequent years. When including costs outside the healthcare sector, like costs of productivity losses, the financial consequences of depression are even larger (7).

Since depression has such a large impact on national healthcare budgets, information on the cost-effectiveness of alternative interventions in depression, aiming to improve the relation between costs and health outcomes, is highly relevant for decision-makers. Various economic evaluations focusing on both psychopharmacological therapies and psychologically oriented interventions for depression have been conducted, but no strong (economic) preference for a single approach can currently be identified (8).

Only a few economic studies specifically focused on the prevention of recurrences, despite the high risk of recurrences in patients with depression and the associated negative long term consequences in terms of both health outcomes and costs (9). The Psycho-Educational Prevention programme (PEP: 10, 11) was developed to improve long term outcomes of patients with depression. This programme was designed to be carried out within primary care settings, where most patients with depression are treated. PEP consists of contacts between patients and prevention specialists, educational meetings on depression management, and telephone monitoring (11, 12, 13). An economic evaluation focusing on the cost-effectiveness of this prevention programme in primary care was performed within the US healthcare system. In contrast to expectations, the study found only modest differences in favour of this programme (14).

The current study was conducted to provide information on the (cost-) effectiveness of PEP in a European healthcare system. The design of the present study differs in several respects from the US study. The PEP programme was slightly adjusted (11, 13) to the situation in the Netherlands. Additional treatment conditions were included in the design, consisting of two enhancements of PEP,

namely the addition of psychiatric consultation (psychiatrist-enhanced PEP), and brief cognitive behavioural therapy (CBT-enhanced PEP). Furthermore, patients were followed during 36 months instead of 12 months.
This paper will present the results of the economic evaluation assessing the cost-effectiveness of three variants of PEP (added to care as usual (CAU)) in comparison with CAU for primary care patients with depression.

Material and Methods

The economic evaluation was part of a 36-month clinical study on the effectiveness of the PEP programme in primary care patients. Details on the design and results of the clinical study are provided elsewhere (13, 15, 16).

Study population and randomisation procedure
Recruitment took place in the northern part of the Netherlands, patients were referred by 49 general practitioners (GPs) working in the catchment area. Inclusion criteria required that patients were aged between 18 and 70, had no life threatening medical condition, and were diagnosed with a current, or only very recently in partial remission, DSM-IV major depression. Patients were excluded when suffering from psychotic disorder, bipolar disorder or dementia, in case of alcohol or drug dependency, when pregnant, or when they were already receiving treatment for depression. Of the 397 patients initially referred by GPs, 267 met study criteria and were subsequently randomised. The applied randomisation procedure (15) was designed to assign most patients to the basic PEP condition and CAU, and less to psychiatrist-enhanced PEP and CBT-enhanced PEP. A sampling ratio of 2:3:1:1 was applied for CAU, PEP, psychiatrist-enhanced PEP, and CBT-enhanced PEP, respectively.

Interventions
Psycho-Educational Prevention programme (PEP): The PEP programme aims to improve the long-term outcome of depression through strengthening the patient's self-efficacy and proactive self-management skills, applying predominantly psycho-educational techniques. Patients attended three individual face-to-face contacts with trained prevention specialists (one psychiatric nurse and two psychologists), followed by telephone monitoring contacts at three month intervals during the 36 months of the study. The PEP intervention, including the

accompanying book and video, was developed by Katon and co-workers (10) and translated and adapted to the Dutch culture and healthcare system (11, 13).
Psychiatric consultation followed by PEP (psychiatrist-enhanced PEP): Before the start of the basic PEP programme, patients had an appointment of one hour with a psychiatrist. The psychiatrist subsequently advised the GP on psychopharmacological treatment of the patient.
Brief cognitive behavioural therapy followed by PEP (CBT-enhanced PEP): Before entering the basic PEP programme, patients attended 10 to 12 individual 45 minute sessions of cognitive behavioural therapy (17), provided by one of three clinical psychologists. At the conclusion of the CBT programme, the therapist informed the prevention specialist about the results of CBT.
Care as Usual (CAU): CAU was provided by the GP. In the Netherlands, treatment of depression by GPs consists of brief supportive counselling, antidepressant prescription, and referral to specialty psychiatric treatment when needed. The variants of PEP provided in this study all included treatment by the GP to assess the additional benefit of PEP.

Outcome measures
Primary outcome measure of the study was the proportion of depression-free time (i.e. the time that the patient did not meet DSM-IV criteria for major depression). This outcome was defined in accordance with the consensus-paper of Frank (18). A depressive episode is defined as 2 consecutive weeks of depression, remission as 2 to 7 consecutive weeks without depression, relapse as 2 consecutive weeks of depression started *within* remission, recovery as 8 consecutive weeks without depression, and finally recurrence as 2 consecutive weeks of depression started *within* recovery. Power analyses were based on expected cumulated relapse/recurrence percentages of 50% in CAU, 30% in basic PEP, 25% in psychiatrist-enhanced PEP, and 20% in CBT-enhanced PEP.
Outcome measures were mainly collected by means of three-monthly interviews during the 36 months of the study. Additional outcomes included mean severity of depression during follow-up, proportion of symptom-free time (i.e. free of all the DSM-IV criteria for major depression), and percentage of patients who relapsed or met criteria for recurrent depression.
The economic evaluation mainly focused on the proportion of depression-free time. The results of additional outcome measures and clinical aspects of the study are presented elsewhere (13, 15, 16).

Costs and unit prices

The economic evaluation was conducted from a societal perspective, costs were assessed both within and outside the healthcare sector. Medical costs that were registered included various types of costs related to inpatient and community care, general healthcare, and medication use. Costs that were relevant for all three variants of PEP included costs related to support provided by prevention specialists trained in PEP, costs of regular telephone contacts with patients, and travel cost of the prevention specialists. In the psychiatrist-enhanced PEP condition, additional costs were related to psychiatric consultation. In the CBT-enhanced PEP condition, cognitive behavioural therapy (10 to 12 sessions by trained therapists) led to additional costs. Costs of travelling and invested time by patients related to the PEP contacts were registered during the study. Costs of invested time were valued in monetary terms based on the net income of a patient. Costs of informal care were based on the monetary valuation of the time invested by relatives or acquaintances in helping or assisting the patient. Additional costs related to the illness, like costs of non-prescribed medication, are referred to as out-of-pocket costs. The friction cost method (19, 20) was applied for estimating costs associated with productivity losses.

Quantities of used resources were registered at three-month intervals for all the patients available at the various times of measurement. The information on costs was primarily collected by means of a questionnaire developed for the current study. This questionnaire assessed, among others, number of admissions to psychiatric hospitals, contacts with psychiatrists and psychologists, sick leave days of patients, and medication use. In order to facilitate comparisons with other economic evaluations, unit prices, i.e. the price of one unit of each included cost type (available on request), were mainly based on Dutch standard prices (21). True costs of used resources were estimated when standard prices were not available. All unit prices were based on the price level of the Euro in the year 2003. Reference prices established for previous years were adjusted to prices of 2003 by applying the consumer price index.

Cost-effectiveness analysis

In cost-effectiveness analysis, costs and the primary health outcome associated with an intervention are used to calculate the incremental cost-effectiveness ratio relative to one or more alternatives (22). The main focus of the current study was on the comparison of costs and health outcomes between patients who received basic PEP and CAU, additional analyses addressed the extended types of PEP (psychiatrist-enhanced PEP and CBT-enhanced PEP). Primary outcome measure used in the cost-effectiveness analysis was the proportion of depression-free time.

In additional economic analyses, Quality-Adjusted Life Years (QALY: 23) were included as primary outcome measure. QALYs combine life years and quality of life into one single outcome measure, and are calculated by multiplying observed survival with utilities. Utilities can be considered as the societal preference for health states. In the present study, raw scores of the EQ-5D (24) assessed at 6-month intervals were transformed into utilities by applying the algorithm of Dolan (25). An important advantage of using QALYs in economic studies is that outcomes can be compared across studies and illnesses.
The method applied for calculating incremental cost-effectiveness ratios (ICER) is provided below (only displayed for basic PEP).

$$ICER = \frac{(C_{PEP} - C_{CAU})}{(PDT_{PEP} - PDT_{CAU})}$$

Where C_{PEP} = mean costs per patient in the PEP group, C_{CAU} = mean costs per patient in the CAU group, PDT_{PEP} = mean proportion depression-free time in the PEP group, PDT_{CAU} = mean proportion depression-free time in the CAU group.

In the standard analyses, costs and health outcomes were discounted by 0%. Alternative discount rates (3% and 5%) were addressed in sensitivity analyses. Uncertainty surrounding the calculated ICERs was examined by the bootstrap method (26). Bootstrapping is an iterative method that consists of randomly selecting patient data (with replacement) from the observed population to create a simulated distribution of data. ICERs were calculated for each of the bootstrap iterations (2000 in the present study), simulated values of the mean estimates for the cost and outcome differences were added to the cost-effectiveness plane (27). Finally, cost-effectiveness acceptability curves (CEACs: 28, 29) were calculated. CEACs inform decision-makers on the probability that an intervention will be cost-effective for increasing monetary values placed on an additional unit of health outcome.

Statistical analysis
Results of longitudinal studies can be biased by missing data due to patients who drop out or are lost to follow-up, especially if their missingness is not completely at random (30). Recently, the potential impact of missing data has also been acknowledged in the area of economic evaluation (31). In the current study, the expectation maximisation (EM) algorithm with a bootstrap approach (32) was applied to deal with patients for whom not all the data were available at the various

measurements. In the current study, the bootstrap method was used to create 2000 simulated patient populations, including patients with missing data. Subsequently, the EM-algorithm was applied for each of these 2000 data sets. The EM algorithm consists of an iterative process, estimating values for missing data based on the observed data. Finally, outcomes of these 2000 derived data sets were combined to estimate overall parameters, like overall means and confidence intervals.
Between-group baseline characteristics were analysed with Student's T-tests for continuous variables and Pearson chi-square tests for categorical variables. P-values less than 0.05 were considered statistically significant. All the analyses were carried out with SPSS 12.0.2 for Windows (SPSS, Inc, Illinois, USA).

Results

Patient characteristics at baseline
Mean overall age of the included patients was 42.8 years (SD=11.3), 65% was female, mean age at first onset of depression was 31.3 years (SD=13.2), 67% suffered from DSM-IV recurrent depressive disorder, and 37% had experienced more than three previous episodes of depression. There were no statistically significant differences in clinical characteristics between groups at baseline (for details see 15). Due to drop-out of patients during the study, results of the conducted longitudinal analyses presented in this paper are based on the data of 226 patients (85% of the initially included patients): 69 in CAU, 107 in PEP, 33 in psychiatrist-enhanced PEP, and 36 in CBT-enhanced PEP. For these patients, relevant cost data could be collected and sufficient information was available to assess the proportion of depression-free time.

Service use and costs
Table 1 shows information on medical and non-medical cost. Means of each cost type are based on available patients per measurement in each group. If a patient did not make use of a specific cost type, costs of €0 were applied when calculating group means. In addition, the percentage of patients who actually used the health services concerned is presented as well. Mean total costs of providing the basic PEP intervention were estimated at €748 per patient. Mean costs of psychiatrist-enhanced PEP and CBT-enhanced PEP were €911 and €1440, respectively. Costs related to care provided by general practitioners are presented separately for each of the intervention groups.

Table 1. Medical and non-medical costs (€) during 36 months

	CAU Mean costs (%[1])	PEP Mean costs (%[1])	Psychiatrist-enhanced PEP Mean costs (%[1])	CBT-enhanced PEP Mean costs (%[1])
Interventions				
Variants of PEP	0 (-)	748 (100)	911 (100)	1440 (100)
(Semi-)inpatient care				
Psychiatric hospital admission	692 (14)	528 (14)	1675 (24)	455 (17)
Psychiatric daycare	27 (6)	57 (10)	113 (19)	53 (10)
General daycare	262 (57)	244 (60)	385 (78)	210 (50)
Outpatient/community care				
Psychiatrist	82 (7)	205 (7)	151 (8)	80 (5)
Psychologist	97 (25)	121 (20)	118 (22)	20 (5)
Social worker	38 (14)	60 (17)	22 (11)	15 (10)
RIAGG[2]	857 (16)	646 (15)	168 (11)	1097 (7)
CAD[3]	0 (-)	19 (4)	0 (-)	0 (-)
Other care for addictions	0 (-)	98 (2)	30 (3)	0 (-)
Other outpatient care	143 (28)	153 (41)	43 (24)	94 (29)
General healthcare				
General practitioner	287 (97)	317 (99)	323 (100)	187 (93)
Physiotherapist	180 (33)	191 (36)	214 (27)	56 (26)
Manual therapist	14 (7)	23 (5)	3 (3)	0 (-)
Chiropractor	0 (-)	11 (5)	0 (-)	0 (-)
Hapto therapist	216 (10)	72 (11)	22 (5)	0 (-)
Home care	20 (17)	19 (11)	35 (16)	6 (7)
Medication				
Prescribed medication	498 (86)	510 (88)	463 (86)	399 (81)
Various non-medical costs				
Travel costs	6 (91)	9 (100)	9 (100)	11 (100)
Time costs	0 (-)	88 (100)	96 (100)	189 (100)
Informal care	154 (58)	189 (57)	125 (68)	100 (43)
Out-of-pocket costs	271 (14)	194 (21)	75 (11)	286 (24)
Productivity losses paid work	3442 (59)	4441 (70)	3896 (68)	3936 (64)
Productivity losses unpaid work	850 (15)	928 (15)	893 (16)	269 (5)

[1] Percentage of patients using the cost type concerned.
[2] Regional institution for mental healthcare.
[3] Consultation Office for Alcohol and Drug Addiction.

Costs that contributed to a large extent to the total amount of costs were costs related to productivity losses, psychiatric hospital admissions, contacts with regional institutions for mental healthcare (RIAGG), and medication use. An overview of mean total costs generated during the study is presented in Table 2.

Table 2. Mean total costs (€) during 36 months

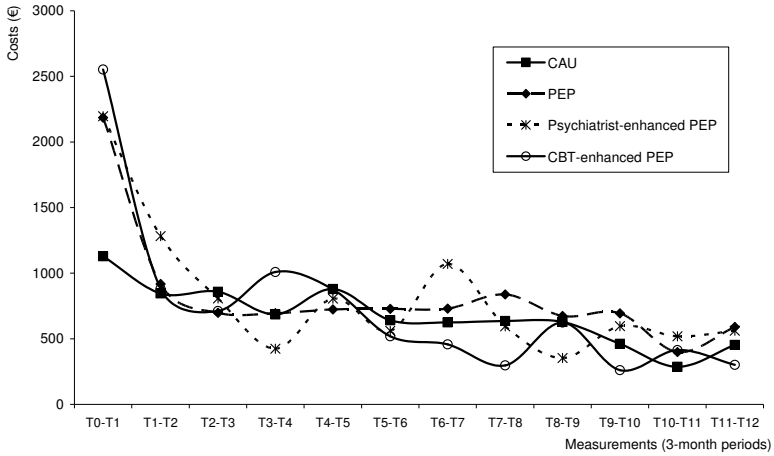
	CAU	PEP	Psychiatrist-enhanced PEP	CBT-enhanced PEP
Mean costs (95% CI) [1]	8200 (6123–10276)	9816 (8128-11504)	9844 (6484-13204)	9254 (5623-12885)

[1] Mean total costs based on the EM algorithm with bootstrap approach. The nonparametric 95% confidence interval is provided between brackets.

These costs were assessed by means of the EM algorithm in combination with the bootstrap method. Mean total costs per patient were €8200 in the CAU group, €9816 in the PEP group, €9844 in the psychiatrist-enhanced PEP group, and €9254 in the CBT-enhanced PEP group. In order to examine the statistical significance of cost differences between groups, nonparametric confidence intervals surrounding the difference scores between CAU and each of the PEP conditions were constructed. Lower and upper boundaries of the confidence intervals indicated that there were no statistically significant differences in total costs between groups (-969 to +4143 for PEP compared to CAU; -2078 to +5810 for psychiatrist-enhanced PEP compared to CAU; -2416 to +4803 for CBT-enhanced PEP compared to CAU).

The course of the mean total costs per group during the 36 months of the study is presented in Figure 1. In the three PEP groups, mean costs generated during the first months of the study were much higher than during later assessments, which is most obvious for the CBT-enhanced PEP group.

Figure 1. Course of mean total costs during the 36 months of the study



These higher initial costs are directly related to the PEP interventions that were mainly provided during the first months of the study. In the CAU group, initial mean costs were only somewhat higher than at later assessments. After the first measurements, mean costs generally decreased over time for all the groups.

Health outcomes

Results of the health outcomes relevant for the economic analyses are presented in Table 3. In contrast to expectations, there were no significant differences between groups in proportion of depression-free time.

Table 3. Proportion of depression-free time and QALY results

Outcome measure	CAU	PEP	Psychiatrist-enhanced PEP	CBT-enhanced PEP	Significance of differences[1]
Mean proportion of depression-free time	.74	.71	.78	.78	n.s.
QALYs [2]	2.31	2.10	2.15	2.27	n.s.

[1] Kruskal-Wallis test due to the skewed distribution.
[2] Derived QALYs are based on the data of 165 patients. CAU: 42, PEP: 70, psychiatrist-enhanced PEP: 27, CBT-enhanced PEP: 26.

The mean proportion varied from .71 to .78, indicating that patients did not meet DSM-IV criteria for major depression for approximately three quarters of the study duration. QALYs were derived from information collected for only some of the included patients (42 in CAU, 70 in PEP, 27 in psychiatrist-enhanced PEP, 26 in CBT-enhanced PEP). It was assumed that, after imputation with the EM algorithm, data of the available patients correctly represented data of patients for whom information could not be collected. Due to the applied approach, QALY results should be interpreted with some caution. If patients would have experienced (nearly) optimal health during the 36 months of the study, QALY values would have been close to three. QALYs varied from 2.10 to 2.31 between groups, with the best outcomes for patients in the CAU group and the worst outcomes for the basic PEP group. Differences between groups in QALYs assessed during the three years of the study were not statistically significant (Kruskall-Wallis test, x^2=4.73, p=.19). Economic analyses focusing on QALY results will not be presented in the current paper. Outcomes of these analyses all favoured CAU, and therefore do not provide any relevant additional information for decision-makers.

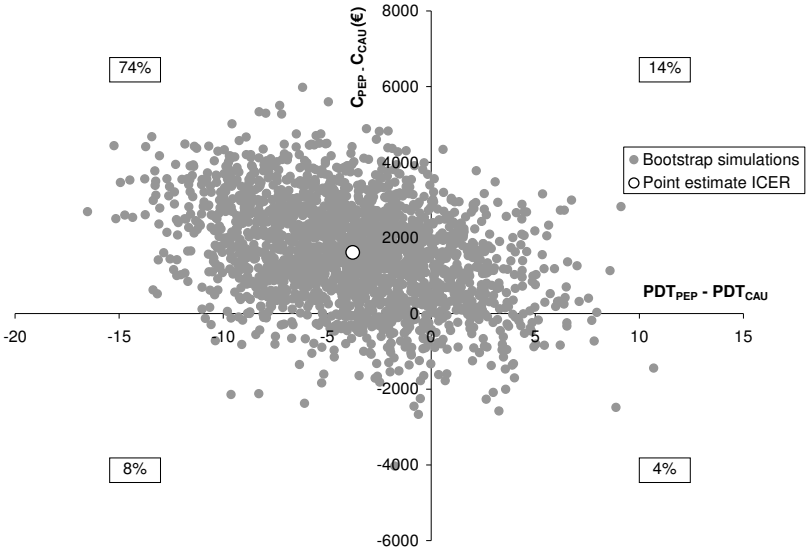
Cost-effectiveness analysis

The point estimate of the ICER and the results of the bootstrap analyses are presented in the cost-effectiveness planes in Figure 2. For the comparison between basic PEP and CAU, the calculated value of the ICER was -€429 per proportion depression-free time (PDT). Here, the negative value indicates that PEP was associated with higher mean costs and worse health outcomes, i.e. was not cost-effective.

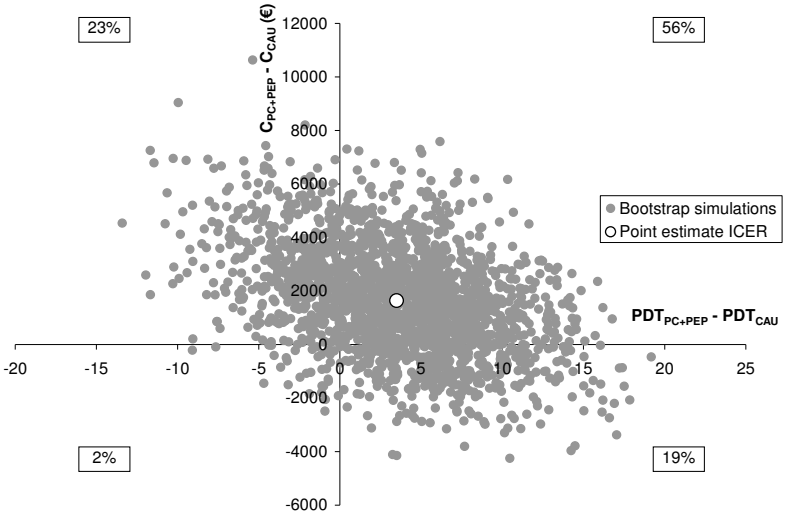
For each quadrant of the cost-effectiveness plane, information is provided on the percentage of bootstrap simulations located in that quadrant. For basic PEP, approximately 74% of the estimated mean cost and effect differences is located in the Northwest quadrant. In other words, CAU dominates basic PEP in 74% of the cases. For psychiatrist-enhanced PEP and CBT-enhanced PEP, the point estimate of the ICER is located in the Northeast quadrant, i.e. cost were higher but health outcomes were better. Interpretation of outcomes in the Northeast (and Southwest) quadrant depends on how much decision-makers are willing to pay for an additional unit of health outcome.

Figure 2. Results of the cost-effectiveness analyses and bootstrap method

A. PEP compared to CAU



B. Psychiatrist-enhanced PEP (PC+PEP) compared to CAU



C. CBT-enhanced PEP (CBT+PEP) compared to CAU

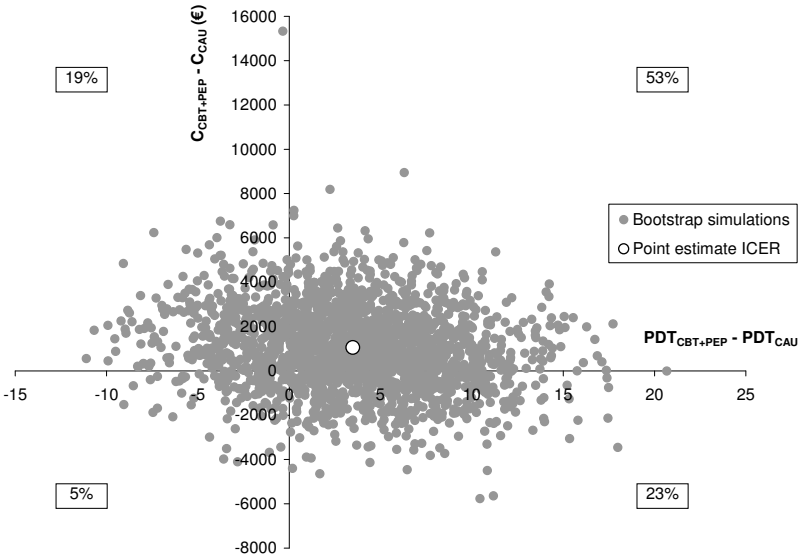
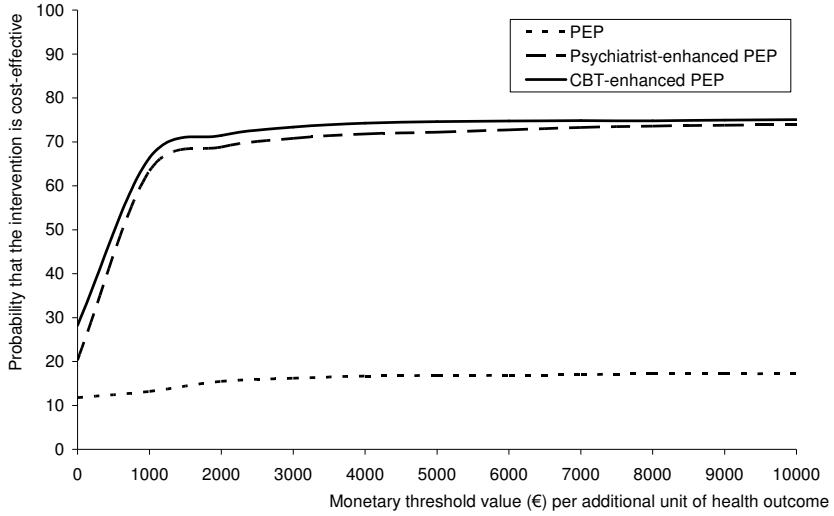


Figure 3 shows the calculated cost-effectiveness acceptability curves, presenting the probability that the various types of PEP will be cost-effective for increasing monetary values placed on an additional proportion of depression-free time.

Figure 3. Cost-effectiveness acceptability curves



Compared to basic PEP, results of psychiatrist-enhanced PEP and CBT-enhanced PEP seem (relatively) more positive. When decision-makers are willing to pay €1000 to €1500 per proportion depression-free time, the probability that psychiatrist-enhanced PEP or CBT-enhanced PEP will be cost-effective increases up to 70%.

Sensitivity analyses

In the first type of sensitivity analysis, discount rates were varied and consequences for differences in mean total costs between groups were studied. Costs were discounted at 3% and 5%, instead of 0% in the standard analyses, results are presented in Table 4.

The influence of discounting slightly differs between conditions, but is most pronounced for CBT-enhanced PEP. The difference between the mean total costs of CBT-enhanced PEP and mean total costs of CAU is approximately €200 less when discounting with 5% instead of 0%. Furthermore, the consequences of excluding costs related to productivity losses from the analyses were examined, due to the inconsistent inclusion of these costs in published studies. Moreover, interpretation of productivity costs in the current study was complicated by an initial difference between groups in the percentage of persons with paid work (49% of the persons in the CAU group had paid work, in contrast to 62% in the PEP group).

Table 4. Sensitivity analyses

Type of analysis	CAU Mean total costs	PEP Mean total costs	psychiatrist-enhanced PEP Mean total costs	CBT-enhanced PEP Mean total costs
Variation of discount rates				
3 %	7941	9647	9568	8750
5 %	7822	9505	9437	8652
Alternative analyses				
Exclusion productivity costs	3856	4509	5087	4569
Complete case approach [1]	7760	8658	9319	10225

[1] The complete case analysis of costs is based on the data of 105 patients (46% of patients included in the standard analyses). CAU: 26, PEP: 44, psychiatrist-enhanced PEP: 20, CBT-enhanced PEP: 15.

Mean total costs were, unsurprisingly, much lower in all the groups when excluding productivity costs. Cost outcomes in this sensitivity analysis were in favour of the CAU group, which is comparable with previous results. Differences in mean total costs between the CAU condition and the other groups were smaller than in the standard analyses.

Additional sensitivity analyses focused on the cost data of 105 patients for whom all the measurements were available (46% of the patients included in the standard analyses). When comparing results of these complete case analyses with the standard analyses presented in this paper, the overall amount of assessed costs shows some changes. Mean costs of patients in the CAU condition were still considerably lower than in the other conditions. However, mean costs of the 15 patients who received CBT-enhanced PEP were now higher than costs of patients in the other PEP groups.

Discussion

This paper presented the results of an economic evaluation examining the cost-effectiveness of three variants of a psycho-educational prevention programme added to care as usual in primary care patients with depression. In contrast to expectations, the basic PEP programme was not cost-effective compared to CAU. Costs of patients who received PEP during the three years of the study were higher and the proportion of depression-free time was lower. Overall, current findings seem comparable to the results of an economic evaluation of PEP situated in the US healthcare system (14), although health outcomes were slightly more in favour of PEP in that study.

Mean total costs generated by the various groups during the 36 months of the study ranged from €8200 to €9844. The total amount of costs was mainly influenced by costs related productivity losses, the PEP interventions, psychiatric hospital admissions, medication use, and visits to regional institutions for mental healthcare. Although indirect costs of depression are not always included in economic studies, the potential economic impact of productivity losses associated with depression has been widely acknowledged (22, 6). In the current study, approximately half of the total costs was related to productivity losses. One of the conducted sensitivity analyses focused on the exclusion of costs related to productivity losses, due to debates on the inclusion and quantification of these costs and initial differences between groups in the proportion of persons with paid work. Outcomes of this sensitivity analysis were in favour of CAU and supported the overall conclusions, but differences in mean total costs between PEP and CAU were smaller. When drawing a comparison between the (yearly) direct medical costs assessed in the current study to previous studies, current findings generally seem comparable (14, 33) or somewhat higher than previously published results (34). Unfortunately, the exact types of (medical) costs included in economic analyses are not always clearly indicated in published papers, which is one of the aspects complicating direct comparisons of costs between studies.

In contrast to earlier studies on the (cost-)effectiveness of PEP, the outcomes of two enhancements of the PEP programme were also examined, namely the addition of psychiatric consultation and cognitive behavioural therapy (CBT). Both alternatives to basic PEP led to better health outcomes than basic PEP, but effect differences with CAU were generally modest while costs were higher. Additional economic analyses indicated that outcomes were slightly more positive for CBT-enhanced PEP than for psychiatrist-enhanced PEP.

Previous studies have shown that CBT has a positive effect in various patient populations with moderate to severe depression (35), and appears to be cost-

effective as well (36, 37). A recently conducted study in primary care patients with depression and comorbid anxiety disorders showed that computer-delivered CBT was associated with lower costs and better health outcomes (38). Based on the results of the current study, it seems unlikely that PEP could make a relevant contribution to improve the (cost-) effectiveness of CBT treatment for depression in primary care. Various possible reasons for the ineffectiveness of PEP have been discussed elsewhere (13, 15, 16).

An important strength of the current study was the long follow-up period of 36 months, during which relevant consequences of the examined interventions could properly be studied. In the available literature, no studies could be identified that addressed the improvement of the long-term outcome of depression in primary care with comparable follow-up periods. Unfortunately, the combination of a long follow-up period and frequent measurements also led to methodological difficulties. Some patients dropped out of the study or became lost to follow-up, for others intermittent measurements were not always available. The negative consequences of missing data for longitudinal analyses have been widely acknowledged (30, 31), and various methodological approaches to account for missing data have been developed. In the current study, the expectation maximisation (EM) algorithm with a bootstrap approach was applied, which appears to be a valid method for handling missing data in economic evaluations (32). Complete case analysis could only be conducted for less than half of the included patients. Results of this alternative analysis generally supported findings of the EM algorithm with bootstrap approach.

The use of QALYs, or comparable generic health outcomes, is strongly preferred from the perspective of a decision-maker. QALYs enable comparisons across studies and illnesses, and are required when constructing (national) league tables aiming to rank healthcare interventions in terms of cost-effectiveness (39). In the current study, QALYs were assessed in addition to the primary outcome measure, the proportion of depression-free time, and were derived from information that could only be collected for some of the included patients. QALY outcomes of patients in the CAU group were better than outcomes in the basic PEP group, which is in line with the results of the primary outcome measure. However, QALY outcomes indicated that patients in CAU were also functioning better than the patients who received psychiatrist-enhanced PEP and CBT-enhanced PEP. Some authors have expressed concerns about the use of QALY outcomes in patients with depression (40), while others have been more positive (41). In general, it seems advisable to interpret QALYs assessed in patients with depressive disorders with some caution, and carefully consider results of additional outcome measures as well. In the context of the results of the current study, there seems to be no reason

to expect that overall conclusions would have been different when QALYs had been collected for all the included patients.

In conclusion, results of the current study indicated that the basic PEP intervention was not cost-effective compared to CAU in primary care patients with depression. The economic analyses focusing on two enhancements of PEP showed somewhat more positive results. Based on the outcomes of this study, there seems to be little support for the implementation of PEP in current healthcare systems. Recently, various studies have demonstrated encouraging (economic) results with several formats of cognitive behavioural therapy in patient populations with depression. Future economic studies situated in different healthcare systems may focus on the long term (cost-)effectiveness of alternative formats of cognitive behavioural therapy in primary care patients with depression, in order to improve the well-being of patients and reduce the considerable societal costs associated with this disabling disorder.

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Chapter 5

Economic consequences of alternative medication strategies in first episode psychosis

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Submitted

Abstract

Background: Although maintenance treatment appears to be successful in preventing relapses in first episode psychosis, it is also associated with side effects and might impair functional outcome. Guided discontinuation strategy is a less intrusive intervention, but may lead to more relapses. In the current economic evaluation, costs and health outcomes of discontinuation strategy were compared with the results of maintenance treatment in patients with first episode psychosis.
Method: The study was designed as a randomised clinical trial with two treatment conditions, guided discontinuation strategy and maintenance treatment. In total 128 patients were prospectively followed for 18 months after six months of stable remission. The economic evaluation was conducted from a societal perspective. Quality-Adjusted Life Years (QALYs) were used as primary health outcome in the economic evaluation. Relapse rates were assessed in addition to various other secondary outcomes.
Results: There were no relevant differences between groups in terms of mean total costs during the main study phase of 18 months. Furthermore, no differences between groups were found for the QALY results. The relapse rate of discontinuation strategy (42%) was twice as high as in maintenance treatment (21%).
Conclusions: There were no indications that either of the examined interventions is superior to the other in terms of costs or QALY results. Additional results indicated that the relapse rate in discontinuation strategy was twice as high, but without an increase in hospital admissions or negative consequences on other clinical outcomes. For a minority of remitted first episode patients, guided discontinuation strategy offers a feasible alternative to maintenance treatment.

Introduction

Current guidelines for the treatment of multiple and first episode psychosis recommend prolonged use of antipsychotic drugs following remission (1, 2). This continuation of antipsychotic drugs is often referred to as maintenance treatment. Although maintenance treatment appears to be successful in preventing relapses, it is also associated with serious drawbacks, including disabling side effects and low compliance (3, 4). Guided discontinuation strategy, consisting of gradually tapering antipsychotic doses and eventually discontinuing antipsychotics if feasible, might offer a less intrusive alternative for maintenance treatment. However, various studies on guided discontinuation in multiple episode patients did not demonstrate the expected advantages like reduced side effects or improved functional outcome, but did find more frequent relapses (5, 6). Consequently, maintenance treatment has generally been considered superior to guided discontinuation for both multiple and first episode psychosis, despite the lack of prospective studies in first episode patients. Research explicitly focusing on guided discontinuation in first episode psychosis was needed, due to remaining concerns about side effects of maintenance treatment, and resistance to continued pharmacological treatment particularly expressed by first episode patients (7). Moreover, there are indications that some first episode patients may not require antipsychotics following remission (8).

A randomized clinical trial (9) was conducted to examine which approach (guided discontinuation strategy or maintenance treatment) achieves the best balance between health benefits and negative side effects in patients with a first psychotic episode. Alongside this clinical study, an economic evaluation was performed to assess and compare the economic aspects of both medication strategies. For decision-makers in the field of healthcare, information on the cost-effectiveness of alternative treatment approaches in first episode patients is highly relevant. Schizophrenia and related psychotic disorders are among the most expensive (mental) illnesses worldwide (10). Approximately 2% to 3% of national healthcare expenditures in Western countries is spent on providing care to these patients. Although most costs associated with psychosis are related to hospitalisation (11), costs outside the healthcare sector can be substantial as well (12, 13). Consequently, interventions like discontinuation strategy, with the potential to be beneficial for patients in an early phase of a serious mental illness, could lead to considerable health gains and reduced healthcare expenses in future years.

The current paper will present the results of the economic evaluation that was conducted alongside the described clinical study. Costs and health outcomes of guided discontinuation strategy will be compared with the results of maintenance treatment in patients with remitted first episode psychosis.

Method

Study population
Recruitment took place in 7 regions in the Netherlands, covering a catchment area of 3.1 million inhabitants. Each of these regions had its own mental health service and research team. All patients having a first contact with mental healthcare due to a first episode of non-affective psychosis were screened by local research teams. Patients were eligible for the study when fulfilling various criteria, including a diagnosis of schizophrenia or related psychotic disorder, aged between 18 and 45, and being responsive to medication (response of positive symptoms) within 6 months after inclusion and sustaining remission for 6 months.

Design of the study and examined interventions
The study was designed as a randomised clinical trial with two treatment conditions, guided discontinuation strategy and maintenance treatment. After inclusion, patients were randomly assigned to one of these conditions. During the first six months, patients in both conditions received comparable treatment, including antipsychotic pharmacotherapy. In guided discontinuation strategy, doses of antipsychotics were gradually tapered in one or two months (starting at 5 months after inclusion) and discontinued if feasible. Maintenance treatment was carried out according to the guidelines of the APA, which entailed the preferred use of second-generation antipsychotics in low dose. The frequency of monitoring was at the discretion of the clinician. In the guided discontinuation group, regular visits at no longer than 3-week intervals were recommended.

Outcome measures and power analysis
The primary outcome measure used in the economic evaluation was the QALY (Quality-Adjusted Life Years: 14). QALYs combine quantity and quality of life into one single outcome measure. The quality component of the QALY consists of the (societal) preference for health states, often referred to as utilities. In the present study, the EQ-5D (15) was used to measure health status in the included patient population. The EQ-5D is a commonly applied self-administered preference-based instrument, consisting of five items that address mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each item can be scored on three levels (no problems, some problems, and extreme problems), resulting in 243 (3^5) possible health states. Utilities were derived from health states measured with the EQ-5D by applying the algorithm of Dolan (16). The conducted power analysis was based on expected utility scores in the patient population under study. In order to have sufficient power (80%) to detect a relevant difference in

utilities (.13) in favour of discontinuation strategy with an alpha of .05, 42 patients were required in each study condition. At least 112 patients had to be included in the trial to account for an expected drop-out rate of 25%.
Secondary outcomes that were assessed included relapse rates, social functioning, psychopathology, side effects and burden on the family. Results of relapse rates will briefly be described in the current paper, for detailed information on additional outcomes the reader is referred elsewhere (9, 17). Measurements took place at the time of inclusion, 6 months after inclusion (following 6 months of stable remission), 15 months after inclusion, and finally 24 months after inclusion.

Costs and unit prices
The economic evaluation was conducted from a societal perspective; costs in and outside the healthcare sector were assessed. Medical costs that were registered included various types of costs related to inpatient care, community care, and general healthcare. Registered (direct) nonmedical costs consisted of costs related to informal care and out-of-pocket costs. Besides informal care consisting of household work, various other forms of support that family members or acquaintances may provide were also included, like the time spent accompanying patients to visit healthcare professionals. Out-of-pocket costs were the various additional costs directly related to the illness, like costs of cancelling holidays due to psychiatric problems. Costs of productivity losses due to illness-related absence from work were estimated by means of the friction cost method (18, 19). In addition, costs of decreased productivity without absence from work were also assessed. Costs related to the inability to perform voluntary work were estimated by hourly wages for professional household workers.
Quantities of used resources were prospectively registered for all the patients included in the study. Most of the information was collected by means of a detailed questionnaire on costs. This questionnaire was administered three times during the study by means of a face-to-face interview with the patient addressing the various measurement periods (T0-T6, T6-T15, T15-T24). The questionnaire assessed, among others, admissions to psychiatric hospitals, contacts with healthcare professionals, and absence from work. Additional information was collected by healthcare professionals involved (for instance, on the use of prescribed medication).
In order to facilitate comparisons with other economic evaluations, unit prices, i.e. the price of one unit of each included cost type, were mainly based on Dutch standard prices (20). True costs of used resources were estimated when standard prices were not available. All unit prices were based on the price level of the Euro

in the year 2004. Reference prices established for previous years were adjusted to prices of 2004 by applying the consumer price index.

Design of the economic evaluation and statistical analysis

The economic evaluation was designed as a cost-utility analysis (21), which is often seen as a special form of cost-effectiveness analysis where health outcomes are expressed in terms of QALYs. The assessment of QALYs has been discussed previously in the section on outcome measures. Various additional analyses, including bootstrap analyses, were planned to provide information on the uncertainty of the results of the economic evaluation. Bootstrapping (22) is an iterative method that consists of randomly selecting patient data (with replacement) from the observed population to create a simulated distribution of data. Furthermore, several sensitivity analyses were scheduled to examine the consequences of variations in discount rates and the exclusion of productivity losses. Sensitivity analyses specifically focused on discounting and productivity losses since there is currently no consensus in the literature on the methodology related to these aspects of economic evaluation.

Analyses of costs and clinical outcomes were conducted in accordance with the 'intention-to-treat' principle, using mixed model methodology (SPSS 12) under the assumption of missingness at random. Mixed models are recommended for longitudinal analyses since all available data can be used, including data of patients for whom not all the measurements are available. Baseline outcomes were included as covariate in the models on costs to correct for initial differences between groups.

Results

Patient characteristics

In total 131 patients were included in the trial. Three patients withdrew informed consent and dropped out of the study. Presented results are based on the data of 128 patients, 65 patients received guided discontinuation strategy (DS group), and 63 patients received maintenance treatment (MT group). Baseline characteristics of these 128 patients are presented in Table 1. No significant differences between groups were found on any of these characteristics.

Table 1. Baseline characteristics of patients included in the analyses *

Characteristics	DS group (n=65)	MT group (n=63)	p value
General characteristics			
Male gender	45 (69.2)	44 (69.8)	.94
Living alone	21 (32.3)	25 (39.7)	.38
Married or cohabiting	11 (16.9)	9 (14.3)	.68
Paid job >16 hrs a week	33 (50.8)	24 (38.1)	.15
Aspects of psychosis and treatment			
Mean age at onset psychosis (SD)	26.0 (6.7)	25.2 (6.6)	.49
Mean age at start of treatment (SD)	26.7 (6.4)	26.0 (6.4)	.52
Mean time to response days (SD)	72.4 (48.5)	78.2 (56.5)	.53
Educational level			
Low	16 (24.6)	15 (23.8)	
Middle	35 (53.8)	36 (57.1)	.92
High	14 (21.5)	12 (19.0)	
Diagnosis (after intake and screening)			
Schizophrenia	25 (38.5)	33 (52.4)	.11
Other non-affective psychotic disorders	40 (61.5)	30 (47.6)	

* Unless otherwise indicated, data are given as a number (percentage) of subjects.

Cost types and healthcare utilisation

Table 2 shows the various medical and non-medical costs generated by both groups during the main phase of the study of 18 months. Furthermore, this table also displays information on the utilisation of healthcare services; the number of patients using each cost type involved is provided.

Costs of admissions to psychiatric hospitals had a substantial influence on total costs (51% and 56% of total costs in the DS and MT group, respectively). In both groups, 18 patients were admitted to psychiatric hospitals during the study. Mean duration of stay in hospitals was longer for patients in the MT group, which resulted in higher mean costs. In the DS group, mean costs of medication use were €575 lower than in the MT group. Costs of the various forms of informal care were considerable in both groups, but most pronounced in the MT condition. Mean costs associated with productivity losses of paid work were higher for patients in the DS group, who more often had paid work at the start of the study.

Table 2. Medical and nonmedical costs (€) during T6-T24

Cost types	DS group (n=65)		MT group (n=63)	
	Mean costs whole group (SD)	Mean costs[1] (N)	Mean costs whole group (SD)	Mean costs[1] (N)
(Semi-)inpatient care				
Hospital admission	10731 (25460)	33981 (18)	15868 (36806)	52011 (18)
Day care	3080 (8458)	12540 (14)	2253 (5080)	12085 (11)
Sheltered accommodation	1839 (9453)	34941 (3)	3155 (11652)	31029 (6)
Outpatient/community care				
Psychiatrist	318 (312)	378 (48)	374 (450)	450 (49)
Psychologist	113 (336)	458 (14)	72 (235)	532 (8)
Social-psychiatric nurse	258 (363)	460 (32)	281 (385)	437 (38)
Social worker	42 (238)	474 (5)	38 (103)	223 (10)
Crisis intervention	26 (80)	244 (6)	25 (96)	293 (5)
Psychiatric home care	135 (479)	1102 (7)	15 (75)	302 (3)
CAD[2]	8 (60)	449 (1)	4 (29)	225 (1)
Other outpatient care	121 (377)	574 (12)	451 (1268)	1266 (21)
General healthcare				
General practitioner	11 (28)	53 (12)	11 (23)	47 (14)
Alternative healthcare	8 (41)	220 (2)	20 (89)	232 (5)
Home care	26 (159)	732 (2)	138 (550)	1624 (5)
Emergency care	5 (37)	281 (1)	7 (41)	211 (2)
Other general healthcare	13 (58)	180 (4)	0 (3)	25 (1)
Day activity institutions				
Day activity centre	138 (442)	713 (11)	147 (372)	577 (15)
Drop-in centre	0 (2)	10 (2)	13 (89)	190 (4)
Other institutions	33 (160)	468 (4)	59 (216)	501 (7)
Medication				
Prescribed medication	1063 (899)	1122 (54)	1638 (1090)	1638 (59)
Non-prescribed medication	17 (52)	78 (12)	33 (133)	328 (6)
Various non-medical costs				
Informal care (household)	439 (1637)	2502 (10)	511 (1769)	2743 (11)
Other informal care	1781 (2936)	2743 (37)	2630 (5238)	4083 (38)
Out-of-pocket costs	30 (139)	428 (4)	15 (62)	151 (6)
Productivity losses				
Paid work	699 (1802)	3623 (11)	307 (1244)	3627 (5)
Unpaid work	99 (430)	942 (6)	159 (757)	1871 (5)
Paid work without absence	76 (325)	1082 (4)	37 (262)	1086 (2)

[1] Mean costs of patients using the cost types concerned (number of patients is provided between brackets).
[2] Consultation Office for Alcohol and Drug Addiction.

Total costs and mixed model analyses

An overview of the total costs during the various measurement periods of the study is provided in Table 3.

Table 3. Total costs (€) during the study

Measurement	DS group			MT group		
	n	Mean total costs (SD)	Median costs	n	Mean total costs (SD)	Median costs
T0-T6 [1]	65	16193 (17889)	9881	59	20439 (20030)	11147
T6-T15	60	11314 (18267)	3515	60	16322 (21738)	6010
T15-T24	62	9903 (18229)	2640	60	12971 (20489)	3095
T6-T24 [2]	57	21107 (32650)	8413	59	28261 (38164)	12566

[1] Measurement period prior to the introduction of the alternative interventions.
[2] Displayed mean total costs during T6-T24 are based on data of patients for whom all the relevant measurements were available (complete cases).

Due to the initial cost differences between groups, costs during T0-T6 were included as covariate in the mixed model analyses. Results of the mixed model analyses focusing on differences in mean total costs during T6-T24 are displayed in Table 4.

Table 4. Costs and QALYs; ANOVA table based on mixed effect analyses[1]

Outcome measure with model effects	df	F	P
Costs			
Effects			
Intervention	(1,118)	1.053	.307
Time	(1,114)	2.064	.154
Intervention * Time	(1,114)	.095	.759
Baseline (T0-T6) costs (covariate)	(1,121)	47.351	<.001
QALYs			
Effects			
Intervention	(1,128)	.493	.484
Time	(7,707)	.927	.485
Intervention * Time	(7,707)	.678	.691

[1] Mixed effect analyses included a random effect of subject. Mixed models on costs were corrected for differences at baseline by means of covariance adjustment.

The effect of the baseline costs included as covariate in the model was significant. There was no significant intervention effect, nor were significant differences detected over time (neither main effect nor interaction between intervention and time).

QALYs

Table 5 shows the means and standard deviations for calculated utilities based on the EQ-5D, as well as derived QALY outcomes.

Table 5. Utilities and QALYs, mean values and standard deviations

Measurement	DS group			MT group		
	n	Utilities (SD)[1]	QALYs[2]	*n*	Utilities (SD)[1]	QALYs[2]
T0	65	0.842 (0.155)	-	62	0.843 (0.180)	-
T3	49	0.862 (0.157)	0.216 (0.030)	43	0.897 (0.127)	0.215 (0.036)
T6	62	0.903 (0.115)	0.218 (0.030)	58	0.848 (0.203)	0.215 (0.037)
T9	60	0.896 (0.135)	0.226 (0.024)	53	0.898 (0.146)	0.219 (0.036)
T12	62	0.887 (0.131)	0.225 (0.026)	57	0.873 (0.193)	0.221 (0.038)
T15	61	0.878 (0.158)	0.222 (0.027)	57	0.860 (0.203)	0.217 (0.046)
T18	60	0.908 (0.136)	0.223 (0.034)	55	0.855 (0.208)	0.215 (0.045)
T21	58	0.869 (0.158)	0.222 (0.031)	58	0.881 (0.172)	0.216 (0.042)
T24	60	0.860 (0.185)	0.215 (0.035)	58	0.867 (0.163)	0.218 (0.034)

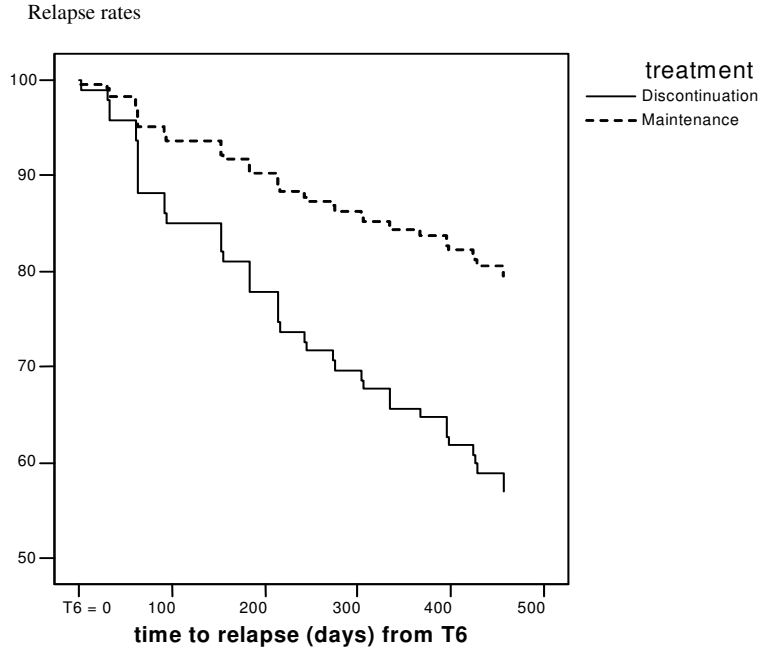
[1] Utilities were calculated by using the algorithm of Dolan to transform EuroQoL scores.
[2] QALYs were calculated based on the mean utility value during a 3-month period prior to the assessment concerned. Life years were not affected in the present study.

There seems to be little variation in QALY results over time, which is partially due to the fact that life years were not directly affected in the current study. Mean estimated QALYs over the two years of the study were 1.75 (SD=0.22) for both groups. Results of the mixed model analyses on QALYs are shown in Table 4. There was no significant effect of intervention or time. Furthermore, there were no indications for relevant differences between groups in QALY results over time, as demonstrated by the non-significant interaction between intervention and time.

Secondary health outcomes

Figure 1 shows the time to relapse for both groups, starting after 6 months of stable remission.

Figure 1. Relapse rates in guided discontinuation strategy and maintenance treatment



In the Cox regression analysis of time to first relapse the proportion of censored cases (no relapse during follow-up) was 58% in the DS group and 79% in the MT group. Accordingly, the relapse rate was 42% vs. 21% in favour of MT. No relevant or statistically significant differences between DS and MT were found on the other secondary outcomes, including psychopathology and social functioning. Discontinuation was not at all feasible in 46% of the patients in the DS group. However, for 21% of the patients in this group antipsychotics were successfully withdrawn without a relapse during the remaining follow-up (against 5% in MT) (9).

Various sensitivity analyses were performed that focused on variations of discount rates and exclusion of productivity costs. Results of these analyses are not presented in this paper since outcomes supported the general findings of the basic analyses; no relevant differences in costs or QALYs between guided discontinuation strategy and maintenance treatment.

Discussion

To our knowledge, the current study was the first economic evaluation conducted alongside a randomised clinical trial comparing discontinuation strategy and maintenance treatment in patients with a remitted first episode psychosis. In contrast to expectations, results of the economic evaluation did not show relevant differences in costs or primary health outcomes (QALYs) between discontinuation strategy and the maintenance condition.

The overall mean total costs of patients during the main study phase of 18 months (following 6 months of stable remission after a first episode of psychosis) were €24,746. The economic consequences of psychotic episodes are particularly clear when examining the 24 months following first diagnosis; the overall mean total costs generated by patients during this period were €42,478. These costs are relatively high compared to costs assessed in previous cost-of-illness studies or economic evaluations (23, 24) in patients with chronic schizophrenia and related (multiple episode) psychosis. In both treatment groups, total costs were largely influenced by costs of psychiatric hospital admissions, which is in line with previous studies (25). As expected, costs of medication use were lower for discontinuation strategy in comparison with maintenance treatment, despite the slowly inclining use of antipsychotics in the guided discontinuation condition towards the end of the study.

When examining results on the primary outcome measure, i.e. QALYs derived from EQ-5D scores, no differences between groups were found. Calculated QALYs and utility scores were in both groups higher than expected based on literature available prior to the study, and did not show much variation over time. The relapse rate during 18 months of discontinuation strategy (42%) was twice as high as in maintenance treatment (21%). The current findings replicate previous results of higher relapse rates due to medication discontinuation in patients suffering from multiple episode psychosis (6). However, the higher relapse rates did not lead to increased hospitalisation in the guided discontinuation group. There were no advantages of guided discontinuation strategy on any of the additionally assessed health outcomes (9).

A limitation of the study concerns the generalisability of present clinical findings and costs to other countries or healthcare systems. The current study was embedded in a low threshold mental healthcare system in the Netherlands. This enabled direct and frequent monitoring of patients and consequently led to a short duration of relapses and most likely reduced the number of hospital admissions as well as associated costs. Furthermore, there are indications that patients included in the trial had better prognostic features than patients who refused participation (9).

This may have led to an underestimation of mean total costs of patients with a first episode of psychosis in the present study, since better prognostic features are usually associated with less healthcare utilisation in subsequent years.
To conclude, there were no clear indications that either of the examined medication strategies in first episode patients is superior to the other in terms of costs or QALYs. The economic consequences of first episode psychosis proved to be considerable; mean total costs were €42,478 during the first two years following diagnosis. Relapse rates were twice as high in the discontinuation strategy group, and the use of antipsychotics could only be successfully discontinued in a minority of the patients. This strategy should therefore not be offered as an alternative to maintenance treatment in all remitted first episode patients. Further research is required to distinguish patients who have a reasonable chance to discontinue from those who definitively need maintenance medication. Guided discontinuation may be considered for patients who are remitted within six months and allow to be closely monitored to limit negative consequences of relapses. In these patients, this alternative medication approach may convey a more conscious attitude towards antipsychotic drugs and their (side) effects, improve compliance, and add to the sense of autonomy.

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Chapter 6

Cost-effectiveness analysis in severe mental illness: outcome measures selection

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Submitted.

Abstract

Background: Most economic evaluations conducted in mental healthcare did not include widely recommended preference-based health outcomes like the QALY (Quality-Adjusted Life Years). Instead, studies were mainly designed as cost-effectiveness analyses that included single outcome measures aimed at a specific aspect of health.
Aims of the study: To raise awareness about the potential problems related to the selection of outcome measures for economic studies in patient populations with severe mental illness. Furthermore, to make suggestions that may prevent these problems in future economic evaluations.
Methods: Data from a previously conducted economic evaluation assessing the cost-effectiveness of the HIT (Hallucination focused Integrative Treatment) intervention in patients with severe mental illness was used for the analyses presented in the current paper. Economic analyses based on the results of the selected primary health outcome (Positive And Negative Syndrome Scale: PANSS) were compared with results based on various other health outcomes assessed during the study, including QALYs.
Results: No relevant differences between groups were found on the single primary health outcome initially included in the cost-effectiveness analysis. In contrast, relevant and significant differences were identified on three of the four additionally assessed health outcomes. Conclusions based on the results of multiple cost-effectiveness analyses and acceptability curves were strongly in favour of the experimental intervention when including these three additional instruments. QALY results did not show differences between groups.
Discussion: Selecting between outcome measures for cost-effectiveness analysis in the field of mental healthcare appears to be an arbitrary process, which may have considerable consequences for the results of economic studies and subsequent policy decisions. It was argued that inconsistent results across the selected primary health outcome and additionally assessed health outcomes should explicitly be presented to decision-makers. Until there is consensus on a preference-based instrument suited for mental healthcare, various QoL instruments could be applied instead of instruments aimed at specific aspects of health.
Implications for Health Policies: Decision-makers in the field of mental healthcare should be careful when interpreting results of economic studies that included single outcome measures aimed at a specific aspect of health. Due to current reservations on the use of QALYs in mental healthcare, QALY outcomes should be considered in the context of the results of additionally assessed health outcomes.

Introduction

Decision-makers in the field of healthcare are confronted with limited resources. As a consequence, priorities have to be set for health programs and interventions, both new and existing ones. Economic evaluation can provide relevant information to aid decision-makers in this complex process of prioritising and seems to be accepted as a useful instrument for rational policy decisions (1). In this context, it is essential that economic evaluations provide valid and reliable information on both costs and health outcomes of alternative interventions. For economic studies in the area of mental healthcare, however, the assessment of health outcomes is associated with complications and considerable controversy.

Guidelines on the design of economic evaluations generally recommend the use of preference-based health outcomes, in particular Quality-Adjusted Life Years (QALYs: 2), which enable decision-makers to compare outcomes across disorders and studies. The QALY combines quantity with quality of life, where quantity is expressed in terms of life years gained from an intervention, and quality as the preference (utility or value) for health states. Although the QALY concept seems highly relevant from a decision-making perspective, there is no consensus on the use of QALYs in economic evaluation (3). In the area of mental healthcare, various specific concerns exist about QALYs. Unsatisfactory results have been found in several studies that tried to measure utilities in mental healthcare, and there are various difficulties related to the valuation of health states measured in people with severe mental illness (4). Moreover, physical aspects are often overrepresented in instruments that are used for deriving QALYs, which seems to make such instruments less relevant for measuring health in mental illness.

Consequently, only few economic studies in mental healthcare actually applied QALYs. By far the most conducted economic evaluations were designed as cost-effectiveness analyses (5) that included single outcome measures aimed at a specific aspect of health (6). The single outcome measure included in cost-effectiveness analysis is assumed to best reflect relevant health consequences of interventions under study. However, selecting between available outcome measures in the field of mental healthcare can be complicated since mental illness, and particularly severe mental illness, often affects multiple domains of health and functioning (7-10). Moreover, the selection of a single outcome measure appears to be influenced by the perspective from which the patient is considered (11-13). Clinicians typically focus on psychiatric symptoms, relatives of the patient may stress the importance of social functioning, while unmet needs in the area of mental healthcare and rehabilitation may be most relevant for the patient. In practice, the primary outcome measure is usually selected by clinicians or clinically oriented

researchers, which often seems to involve rather arbitrarily choosing one relevant aspect of health over another. Unfortunately, the relevance of a selected primary health outcome for policy decisions (14) is not always taken into account.
In the current paper, the potentially negative consequences of selecting between various outcome measures for economic evaluations in mental healthcare will be illustrated by the results of a previously conducted cost-effectiveness analysis in patients with severe mental illness.

Method

Design economic evaluation
Analyses presented in this paper were based on the data of a study focusing on the cost-effectiveness of the HIT (Hallucination focused Integrative Treatment) programme in patients with schizophrenia and a history of persistent auditory hallucinations (15). HIT integrates cognitive behaviour therapy with various additional forms of intervention, including psycho-education and single family treatment (16). In total 76 patients were randomly assigned to two treatment arms, HIT or care as usual (CAU). The HIT programme was provided during the first 9 months of the study and consisted of approximately 11 contacts with HIT therapists in addition to regular care. CAU was not standardised in the present study and mainly consisted of home visits, psychiatric and social management, and maintenance of medication. The economic evaluation was performed from a societal perspective, i.e. a wide range of costs in and outside the healthcare sector was registered. Medical costs that were assessed included costs of hospital admissions, medication use, and contacts with various healthcare professionals. Costs outside the healthcare sector included costs of informal care, travel costs, and costs related to productivity losses. The Positive And Negative Syndrome Scale (PANSS; 17) was selected as the primary outcome measure during the design phase of the study. The PANSS is a 30-item, semi-structured interview with the patient on psychiatric symptoms (including hallucinations). Power analyses were based on characteristics of the PANSS in the patient population under study. Health outcomes and costs of included patients were registered prospectively during a period of 18 months. Measurement took place at nine-month intervals, starting at the time of inclusion (T0, T9, T18). Since the economic evaluation was an integral part of a clinical study on HIT (18-20), several additional instruments were administered at the same time as the PANSS to assess a range of relevant clinical aspects. Outcomes that were assessed included social functioning,

subjective burden of auditory hallucinations, and Quality of Life (QoL). Experienced researchers were responsible for the interviews with patients and the administration of questionnaires. Results were based on the data of 83% (n=63) of the initially included patients for whom all the relevant costs and health outcomes could be assessed during the study. Longitudinal analyses were conducted in accordance with a complete case approach, no imputation techniques were applied.

Instruments

Main characteristics of the additionally administered instruments are briefly discussed to provide the necessary background information. The Groningen Social Disabilities Schedule (GSDS; 21) is a valid and reliable semi-structured observer-rated interview that addresses social functioning. Total scores of the 7-item version of the questionnaire can range from 0-21. The Auditory Hallucination Rating Scale (AHRS, 22) is a widely used semi-structured interview with satisfactory psychometric properties. The AHRS measures the subjective burden of auditory hallucinations, control over voices and interference with daily functions. Total scores of the AHRS vary between 0 and 32. The EuroQol instrument (23) is a self-administered QoL questionnaire commonly applied in economic studies, consisting of five items that address mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. EuroQol results were transformed into utilities by applying the algorithm of Dolan, which is based on the valuation of health states by the general population (24). Subsequently, QALYs were derived by combining utilities with life years. The World Health Organisation Quality of Life (BREF) assessment (WHOQoL-BREF; 25) is a well-validated 26-item version of the WHOQoL-100 instrument and measures four domains of QoL, i.e. physical, psychological, social, and environment. Outcomes of the abbreviated instrument can be transformed to a scale ranging from 0 to 100.

Lower scores on the PANSS, AHRS, and GSDS indicated a better health status. Accordingly, patients who improved during the study had lower scores on these instruments at the last follow-up (T18) compared to the baseline assessment (T0). In the current paper, change from baseline scores (T18 minus T0) calculated for these instruments were multiplied by -1 to represent an improvement in functioning by positive difference scores. This facilitated comparisons with other studies where better health status is typically represented by higher scores and positive change from baseline scores.

Economic analyses and data analytic procedures

Incremental cost-effectiveness ratios (ICERs) were calculated for each of the administered instruments, mean cost and effect differences were presented in cost-

effectiveness planes (26, 27). Furthermore, bootstrap simulations addressed uncertainty surrounding the calculated ICERs (28). Bootstrapping is an iterative method that consists of randomly selecting patient data (with replacement) from the observed population to create a simulated distribution of data. ICERs were calculated for each of the bootstrap iterations (5000 in the present study), and simulated values of the mean estimates for the cost and outcome differences were presented in cost-effectiveness planes. Cost-effectiveness acceptability curves (CEACs; 29, 30) were based on each of the assessed health outcomes. CEACs provide information on the probability that an intervention will be cost-effective, depending on what decision-makers are willing to pay for an additional unit of health outcome (monetary threshold value). Differences in health outcomes between groups were analysed by Student's T-tests focusing on change from baseline scores.

Results

Cost-effectiveness analysis

In this section, a summary of the most relevant results of the cost-effectiveness study focusing on the HIT intervention is provided. For a detailed description the reader is referred to the original publication (15). Table 1 presents the outcomes on the PANSS and the total costs of both groups during the study.

Table 1. PANSS outcomes and costs (T0-T18)

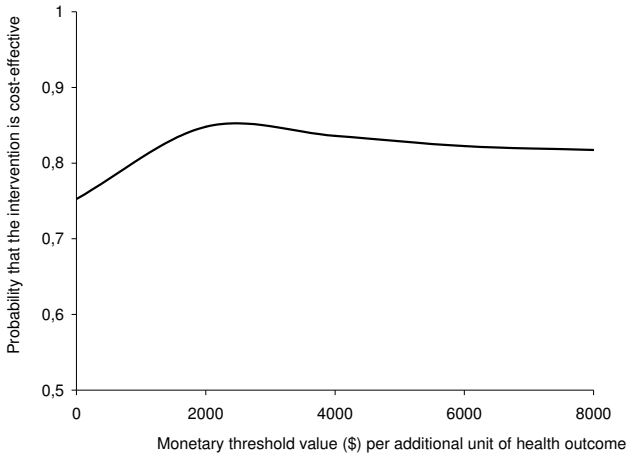
Outcome	HIT (n=31) Mean	CAU (n=32) Mean	Significance of difference (95% CI)[3]
PANSS			
T0	57.1	60.2	
T18	51.1	57.3	
Change from baseline[1]	6.1	2.9	n.s. (-4.23, 10.55)
Costs[2]			
Mean costs	18,237	21,436	n.s. (-12,050, 6,637)

[1] Positive change from baseline scores indicate improved functioning.
[2] All costs are in US dollars (price level of 2000).
[3] Student's T-test for independent samples. Lower and upper limits of the 95% confidence interval of the difference in means are provided between brackets. For costs, the nonparametric 95% confidence interval was assessed with the bootstrap method. Limits of the confidence interval indicated a not statistically significant difference in costs between groups.

Outcomes on the PANSS were slightly in favour of the HIT group (3.2 difference in change from baseline scores on a score range of 30-210). However, these differences were neither clinically relevant nor statistically significant. The mean costs of patients in the HIT group ($18,237) were lower than the mean costs of patients who received CAU ($21,436). The value of the calculated ICER was –$936 per point improvement on the PANSS. This negative value indicated that patients in the HIT group generated fewer costs and had better results on the PANSS. In additional analyses, bootstrap simulations were conducted. The HIT intervention dominated CAU in approximately 60% of the cases. In Figure 1, the cost-effectiveness acceptability curve (CEAC) based on the outcomes of the performed bootstrap analysis is presented. Increasing monetary threshold values per additional unit of health outcome first led to a slightly increasing probability that the HIT intervention would be cost-effective, but this probability never exceeded the 85% level. For values over $2,000 the probability slowly decreased towards 79%, due to the location of the joint density in the north-east and south-west quadrants of the cost-effectiveness plane (30).

Based on the presented results, it was concluded that differences in costs and health outcomes were in favour of HIT and seemed relevant from a decision-makers perspective. A statistically significant cost-effectiveness advantage of HIT over CAU could not be demonstrated.

Figure 1. Cost-effectiveness acceptability curve for PANSS outcomes



Additional health outcomes and cost-effectiveness analyses

The results of the outcome measures that were assessed in addition to the PANSS are summarised in Table 2, for a detailed description the reader is referred to the published outcomes of the clinical study (18, 20).

Table 2. Results of the additionally assessed outcome measures (T0-T18)

Outcome measures	HIT (n=31) Mean (SD)	CAU (n=32) Mean (SD)	Significance of difference (95% CI) [3]
GSDS			
T0	10.2 (4.2)	11.3 (4.8)	
T18	7.4 (4.1)	10.6 (4.2)	
Change from baseline[1]	2.8 (3.2)	0.7 (3.9)	p<.05 (0.35, 3.96)
WHOQoL-BREF[2]			
T0	57.6 (8.0)	59.3 (9.2)	
T18	62.9 (9.7)	58.9 (12.0)	
Change from baseline[1]	5.4 (10.3)	-0.4 (10.9)	p<.05 (0.29, 11.23)
AHRS			
T0	24.7 (3.9)	23.5 (4.8)	
T18	14.2 (8.3)	19.2 (9.8)	
Change from baseline[1]	10.5 (9.1)	4.3 (9.0)	p<.01 (1.58, 10.70)
QALYs			
T0 – T9	0.5 (0.2)	0.5 (0.2)	
T9 - T18	0.5 (0.2)	0.5 (0.2)	
Total QALYs	1.0 (0.3)	1.0 (0.3)	n.s. (-0.15, 0.14)

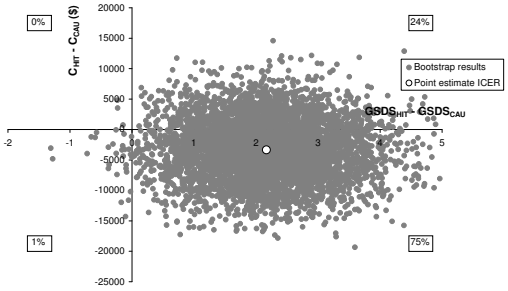
[1] Positive change from baseline scores indicate improved functioning.
[2] n=30 in both groups.
[3] Student's T-test for independent samples. Lower and upper limits of the 95% confidence interval of the difference in means are provided between brackets.

Differences between groups are presented in terms of 'change from baseline scores' on the additionally assessed outcomes, i.e. social functioning, QoL, and subjective burden of auditory hallucinations. Results of the GSDS showed that social functioning of patients in the HIT group improved significantly (p<.05) compared to the CAU group. On the WHOQoL-BREF, a statistically significant difference in terms of improvement in QoL (p<.05) was found in favour of the HIT group. Outcomes on the AHRS indicated that the level of distress decreased and the control over voices increased significantly in the HIT group compared to the CAU group (p<.01). However, QALY results (based on utilities derived from the EuroQol) did not show relevant differences between groups. Costs were already presented in the first part of the results in Table 1.

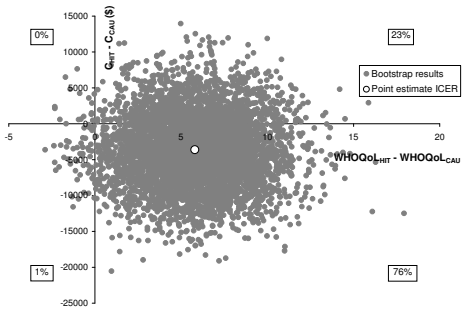
ICERs were calculated based on the outcomes of these four additional outcome measures, followed by bootstrap analyses (results are presented in Figure 2).

Figure 2. Results of economic analyses based on the GSDS, WHOQoL-BREF, AHRS and QALY outcomes

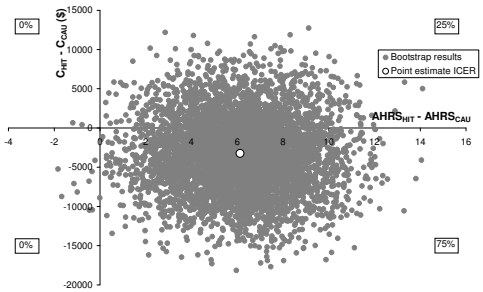
A. GSDS



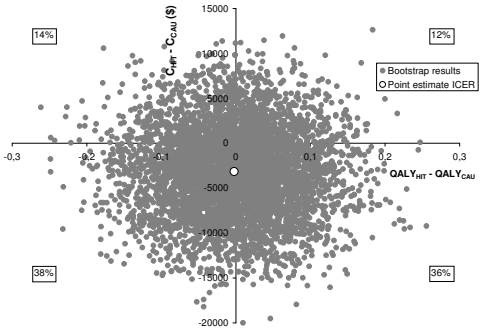
B. WHOQoL-BREF



C. AHRS



D. QALY



For the GSDS, WHOQoL-BREF, and the AHRS, the HIT intervention dominated CAU in approximately 75% of the bootstrap replications. Virtually all the bootstrap outcomes were restricted to the right side of the plane, emphasising significant differences in health outcomes between groups. For the QALY results, bootstrap outcomes were more evenly distributed across the plane, which indicated that there were no relevant differences.

Figure 3 presents the CEACs calculated for the GSDS, WHOQoL-BREF, AHRS, and QALY outcomes. Please note that the four presented CEACs cannot directly be compared, because score ranges of the applied instruments vary. For instance, one (additional) unit of health outcome on a range of 0-20 (GSDS) should be

interpreted differently compared to one unit on a range of 0-100 (WHOQoL-BREF).

Figure 3. Cost-effectiveness acceptability curves

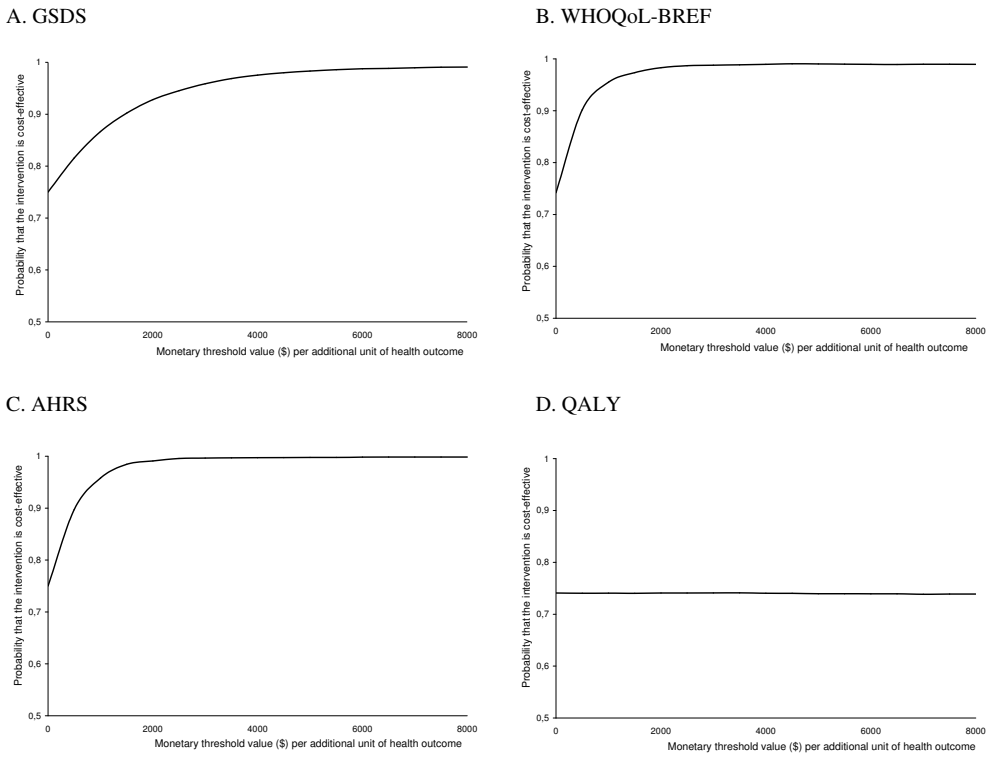


Figure 3 shows that if a decision-maker is willing to pay $2,000 for an additional unit of health, the probability that HIT would be cost-effective tends towards 100% for both the WHOQoL-BREF and the AHRS. The CEAC for the GSDS demonstrated the same trend, but the monetary threshold value placed on an additional unit of health outcome would be slightly higher. The CEAC for the QALY results suggested that the probability of cost-effectiveness was indifferent to monetary threshold values up to $8,000 per QALY gained.

Discussion

Although it is strongly recommended to use preference-based outcome measures in economic evaluations, most studies in mental healthcare included outcome measures aimed at a specific aspect of health (6). The current paper focused on the difficulties associated with the selection of a single primary outcome measure in severe mental illness. These difficulties were illustrated by an economic evaluation that examined the HIT intervention in patients with schizophrenia and persistent auditory hallucinations. Results of the conducted cost-effectiveness analysis, with the PANSS as single primary outcome measure, were presented. Subsequently, an overview was provided of the results of the additionally assessed health outcomes, i.e. the GSDS (social functioning), WHOQoL-BREF (quality of life), AHRS (burden of hallucinations), and QALYs. Subsequently, ICERs were calculated, the bootstrap method was applied to assess uncertainty, and cost-effectiveness acceptability curves were estimated for all the measured health outcomes and costs. Results of the economic analyses based on the GSDS, WHOQoL-BREF, and the AHRS were in favour of HIT and seemed highly relevant from a decision-making perspective. In contrast, differences between groups were less obvious for economic analyses based on the PANSS, and nearly absent for QALY outcomes.

The inconsistency of results across health outcomes illustrates the problems that may arise for economic evaluations in mental healthcare when selecting between different outcome measures. In the presented study, decision-makers would have received insufficient information if only the results of one of the outcome measures had been available. Depending on the health outcome available, policy decisions could have ranged from strongly favourable to indifferent towards the implementation of HIT in current healthcare systems. Therefore, it seems important for economic analysts to at least describe inconsistencies in (additionally) assessed health outcomes when reporting results to decision-makers. Moreover, including conflicting results in supplemental economic analyses may provide relevant additional information. In the literature, there are indications that the inclusion of various outcome measures in economic evaluation is considered to be more informative for decision-makers than strictly focusing on a single outcome measure as is traditionally done in cost-effectiveness analysis (31, 32). Awareness of inconsistencies in health outcomes seems to be highly relevant for the policy-making process. In some situations, decision-makers may eventually have to conclude that adequate policy decisions cannot be based on presented results, due to such inconsistencies.

The finding that QALY outcomes did not demonstrate clear differences between groups, in contrast to three of the other outcome measures, was difficult to

interpret. In the presented study, the quality component of the QALY consisted of utilities derived from the EuroQol questionnaire. Results showed that there were no clear differences between groups in terms of utilities. The quantity component of the QALY, life years gained, was not directly affected; none of the included patients died during the study period. A closer examination of the current results revealed that utilities based on the valuation of (EuroQoL) health states by the general public seem to be particularly insensitive for changes in health of patients with mental illness (19). Various concerns related to the use of QALYs in mental healthcare have already been expressed in the literature (4). Although the EuroQol is among the most widely used instruments for assessing QALYs in economic evaluations, there are no publications available that adequately examined the validity of this instrument (or derived QALYs) in the area of mental healthcare. The mere absence of such studies was recently also noted by Lewis and colleagues (33), who strongly recommended research on the validity of the EuroQoL in patients with severe mental illness. Current findings seem to further support their claim for adequate research on this topic. Clarity on the validity of this instrument in mental healthcare may contribute to changing the present reluctance of mental healthcare professionals to apply preference-based outcome measures.

Most published economic studies in the area of mental healthcare have focused on primary health outcomes aimed at specific aspects of health. Although such outcomes are relevant from a clinical point of view, they cannot always provide decision-makers with information that is useful for policy decisions. The overall well-being (or QoL) of an individual is considered to be a much more relevant indicator for the effectiveness of an intervention for decision-makers. There are various instruments available that can accurately assess QoL. In the presented study, the WHOQoL-BREF was one of the administered questionnaires, which is considered to be a reliable and valid generic QoL instrument, both in patients with somatic and mental illnesses (34). Furthermore, disease-specific QoL instruments have been developed for a wide range of mental illnesses and disorders. It should be noted that QoL instruments are only directly applicable in cost-effectiveness studies if results can be expressed in a single overall score. Reliable and valid QoL instruments fulfilling this requirement may currently be considered as a useful alternative for instruments addressing specific aspects of health in cost-effectiveness analyses in mental healthcare.

To conclude, by far the most economic evaluations in mental healthcare were designed as cost-effectiveness studies focusing on single primary health outcomes aimed at a specific aspect of health, instead of preference-based outcomes recommended by guidelines. Selecting between single primary health outcomes for cost-effectiveness analysis may have considerable consequences for the results of

economic evaluations and subsequent policy decisions. Inconsistency of results across the selected primary health outcome and additionally assessed clinical health outcomes should at least be presented to decision-makers, since awareness of this inconsistency could be highly relevant for the decision-making process. For the moment, researchers or clinicians planning to conduct economic studies in mental healthcare may consider to use QoL instruments instead of instruments focusing on specific aspects of health. Since there are advantages related to the use of preference-based outcomes in economic evaluations, it is important to adequately assess the validity of instruments like the EuroQoL and eventually reach consensus on the use of preference-based outcomes in mental healthcare.

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Chapter 7

Discussion

The economic evaluations presented in this thesis focused on interventions for persons who were diagnosed with major depressive disorder or schizophrenia. These disorders are considered to be among the most disabling (mental) illnesses, and are both associated with intensive healthcare utilisation and considerable costs for society. At the time when the presented studies were initiated, detailed information on economic aspects of interventions in mental healthcare was virtually absent for the Netherlands, and economic studies in the described patient populations were strongly needed to support policy decisions. The primary aim of the conducted studies was therefore to assess the cost-effectiveness of the interventions concerned and report results to decision-makers.
In the following section, the overall findings and interpretation of the economic evaluations that are part of this thesis will be discussed. The policy decisions that were based on these results will also be provided. Various methodological issues encountered in these evaluations will be presented in the context of the current literature. Based on the discussed methodological issues, recommendations will be made for the general design of future economic evaluations in the field of mental healthcare. Finally, recent (inter)national developments and economic benefits related to various other interventions studied in mental healthcare will be discussed, together with the relevance of improving the actual implementation of cost-effective interventions.

Overall findings and the interpretation of results

Chapters 2 through 5 presented the results of four cost-effectiveness studies in patients with major depressive disorder or schizophrenia. In these studies, a wide variety of interventions was compared with care as usual (CAU) in the patient populations concerned. Two interventions were aimed at depression: Cognitive Self-Therapy (*Chapter 3*) and a depression recurrence prevention programme (PEP: *Chapter 4*). The other two studies addressed interventions in patients with schizophrenia: Hallucination focused Integrative Treatment (HIT: *Chapter 2*) and guided discontinuation strategy (*Chapter 5*).
For two interventions (HIT and Cognitive Self-Therapy), costs and health outcomes were in favour of the interventions under study, although differences with CAU in terms of primary health outcomes were generally modest. Results of the study comparing three variants of PEP with CAU showed that basic PEP was associated with higher costs and worse health outcomes than CAU. Two enhanced versions of PEP (with psychiatric consultation and cognitive behavioural therapy)

also led to higher costs, but results of the primary health outcome were slightly better than in CAU. In the study on discontinuation strategy, no relevant differences could be found for costs or health outcomes when comparing results with CAU.

Besides simple comparisons of costs and health outcomes, various additional economic analyses were performed in the presented studies. These analyses included the calculation of incremental cost-effectiveness ratios as well as bootstrap analyses to provide information on the uncertainty surrounding the economic results. Furthermore, cost-effectiveness acceptability curves were assessed in most studies, which provided information on the probability of the interventions being cost-effective. This probability is based on what a decision-maker (or society) is willing to pay for an additional unit of health outcome (1).

Interpretation of the overall results of the various conducted economic analyses depends on whether one adopts a Bayesian decision-making framework, or applies a classical frequentist (statistical hypotheses testing) approach for inference (2). When using a frequentist approach, none of the interventions examined in this thesis can be considered cost-effective, i.e. there were no statistically significant differences for combined cost and health outcomes in any of the four studies. In fact, only few published economic evaluations would fulfil such frequentist criteria. Various authors have strongly argued for a Bayesian approach in recent years, which allows for probability statements that seem more relevant and appropriate in the context of decision-making (3). When interpreting the current results from a Bayesian perspective, HIT appears to be a cost-effective intervention for patients with persistent auditory hallucinations in comparison with CAU. Furthermore, the results of the economic analyses in the Cognitive Self-Therapy study are in support of implementing this intervention in the Dutch healthcare system. Interpretation of the economic results of the study on PEP is not favourable for the basic PEP intervention. Finally, the economic evaluation of guided discontinuation strategy provides no clear economic support for implementing such an approach, although there appear to be clinical advantages related to guided discontinuation for some of the studied patients.

The primary aim of the studies presented in Chapters 2 to 5 was to inform decision-makers on the cost-effectiveness of the interventions under study. The results of these four studies have been reported to the Dutch Ministry of Health, Welfare and Sport. Two of the examined interventions (HIT and Cognitive Self-Therapy) were eventually recommended for reimbursement within the Dutch healthcare system.

Methodological issues related to economic evaluation in (mental) healthcare

In this section, various methodological issues encountered in the presented studies will be discussed. Some are more specific for economic studies in the field of mental healthcare, whereas others have a broader scope.

Outcome measures: QALYs versus (disease-)specific health outcomes
Guidelines on the design of economic evaluations uniformly recommend the use of preference-based health outcomes, in particular Quality-Adjusted Life Years (QALYs: 4). An important advantage of such outcomes is the possibility of directly comparing findings across studies and illnesses. As described in *Chapter 6*, only few published economic evaluations in mental healthcare actually included QALYs (5, 6), due to various methodological concerns about this outcome measure (7).
QALYs were assessed in three of the four economic evaluations presented in this thesis. In the study on guided discontinuation strategy (*Chapter 5*), QALYs formed the primary outcome measure. No differences were found between QALY results of the two study groups, which was in line with the results of various (secondary) clinical outcome measures. For the other two studies (HIT in *Chapter 2*, PEP in *Chapter 4*), QALYs were assessed in addition to the primary health outcomes on which power analyses were based. In the PEP study, QALYs could only be assessed for some of the included patients, results generally seemed to be in accordance with other outcome measures favouring CAU over the basic PEP intervention. However, QALY results were not always consistent with other results. In additional economic analyses (*Chapter 6*) based on data collected during the HIT study (*Chapter 2*), the results of the primary health outcome selected during the design stage were compared with several other health outcomes, including QALYs. Statistically significant (and clinically relevant) differences between study groups were found on three of the additionally administered clinical outcome measures, but differences were absent for QALY results. The studies presented in this thesis were not designed to assess the validity of QALYs in the context of mental healthcare, and can therefore not lead to conclusions on this topic. In general, it seems advisable to interpret QALY results with some caution in patients with mental illness. As also stated by others (8), economic evaluations should never solely rely on QALYs, but at least carefully consider the results on additional clinical outcome measures as well.
Most economic evaluations conducted in mental healthcare had been designed as cost-effectiveness studies that included single outcome measures aimed at specific aspects of health (5, 6). Using such outcomes could be valid in some situations, for instance when an intervention has a very specific objective and effects are only

expected on a well-defined aspect of health (9). However, for many (economic) studies in mental healthcare this will not be the case, and decision-makers could subsequently be provided with incomplete (and sometimes incorrect) information, as illustrated in *Chapter 6*. It was suggested to try to aim for the use of instruments assessing overall well-being or Quality of Life (QoL), by means of generic QoL instruments, or otherwise disease-specific QoL instruments. However, in order to allow priority decisions by decision-makers on a broader or even national level, for instance by means of league tables for comparable or related illnesses (10), the same (preference-based) outcome measure has to be applied in all the studies concerned. For advocates of such an approach, it is important to eventually reach consensus among economic analysts and clinicians in the field of mental healthcare on the use of a generic (preference-based) health outcome in economic evaluation. League tables are currently not explicitly used in the decision-making process in the Netherlands, where reimbursement decisions generally concern alternative interventions directly compared in a specific economic evaluation. In the present situation, it seems to be more important that a primary health outcome applied in economic evaluation can reliably assess (changes in) health in specific patient populations, than to enable comparisons across various illnesses or economic studies.

Power analysis and clinical differences between study groups

Due to ethical reasons, power analyses in economic evaluations are usually based on clinical outcomes in the patient population under study, and not on costs (11). Consequently, most economic studies are underpowered to identify statistically significant differences in costs, since the skewed distribution of costs (and high variance) requires larger sample sizes than comparisons of clinical outcomes.

For three of the four presented studies (HIT, Cognitive Self-Therapy, PEP), power analyses conducted during the design stage of each study were based on characteristics of outcome measures aimed at specific aspects of health in the patient populations under study. In the fourth study (discontinuation strategy), power analyses focused on utilities from which QALYs were derived. Unexpectedly, in none of the studies could significant differences between groups be demonstrated on the primary health outcome, despite the fact that sample sizes were in accordance with performed power analyses.

There are various possible explanations for the absence of expected significant differences on primary outcome measures. In all the studies, the interventions were compared with CAU as provided by healthcare professionals in the Netherlands. In practice, there appeared to be a large variety in treatments provided under the heading of CAU. Many patients in the CAU conditions received more intensive

treatment than expected, which might explain the smaller differences between CAU and the studied interventions. Furthermore, analyses were mainly conducted in accordance with the intention-to-treat principle, i.e. all patients were included in the analyses regardless of whether they continued in the trial or received the intervention to which they were randomly assigned. This is by many considered to be a justified pragmatic approach for analysing data of trials (12). However, it is most likely to lead to lower estimates of the effect of (experimental) interventions than in more controlled settings, like for instance in pilot studies. In several studies, power analyses were based on information collected in pilot studies, where patient drop-out was limited and practically all the patients received the examined intervention. In a recent paper (13), it was demonstrated that actual effect sizes are commonly overestimated in pilot studies, which may lead to underpowered randomised clinical trials. A careful and more conservative interpretation of the results of pilot studies may lead to better estimates of required sample sizes.

Another aspect that is relevant for the discussion on power analyses and clinical differences concerns the design of a study. All the four studies presented in this thesis were designed as superiority trials. A superiority design is applied when researchers expect to find relevant and significant clinical differences between study groups receiving different interventions or treatments. Alternative study designs are less common for clinical trials, but may be more relevant in some situations (14). When an intervention is expected to be associated with clinical effects comparable to standard treatment, but at the same time may lead to other (economic) benefits, one could consider using a non-inferiority design. Non-inferiority designs intend to show that an intervention is at least equal to an alternative in terms of effectiveness (15). Based on a recent literature overview (16), it seems that a non-inferiority design would be appropriate for (economic) studies on self-help treatments or therapies.

Length of follow-up periods and registration of costs

Follow-up periods of economic evaluations should be long enough to adequately capture relevant consequences of examined interventions. Unfortunately, many economic evaluations conducted in mental healthcare followed patients for only a limited amount of time. For instance, the time horizon of various published economic studies in patients with depression and comorbid anxiety disorders typically ranged from 3 to 8 months (17, 18). Conclusions based on such short study periods should be interpreted with caution, especially since initial positive consequences of psychiatric interventions may diminish over time (19).

The follow-up duration of the studies presented in this thesis ranged from 18 (HIT, Cognitive Self-Therapy, discontinuation strategy) to 36 months (PEP). Shorter

follow-up periods would have overestimated either clinical or economic benefits related to the HIT and the Cognitive Self-Therapy intervention, respectively. In the HIT study, there was a statistically significant difference between groups after 9 months on the primary outcome measure in favour of HIT, which was, however, no longer present at 18 months after inclusion. In the study on Cognitive Self-Therapy, healthcare utilisation decreased substantially in both study groups between 6 and 12 months after inclusion, which was most pronounced in the Cognitive Self-Therapy group. However, costs increased again for both groups in the last 6 months of the study. From the current findings, it seems that follow-up periods of at least 12 to 18 months should be used for economic studies in the field of mental healthcare. When focusing on specific symptoms or signs of mental illness expected to occur over a longer period of time, like recurrences or relapses in depression (20, 21), even longer follow-up periods may be indicated.

In all the presented studies, most information on relevant cost aspects was collected by means of a questionnaire, administered to the patients in a face-to-face interview setting. The reliability of information on costs gathered with questionnaires appears to be negatively related to the recall period applied, as suggested by a recent study (22). In that study, it was concluded that recall periods of questionnaires should not exceed the previous 6 months. This was the case for two of the studies included in this thesis. Questionnaires focused on the previous 6 months in the Cognitive Self-Therapy study, and on the previous 3 months in the study on PEP. In the studies on HIT and discontinuation strategy, recall periods were confined to the previous 9 months. Since the questionnaires were administered in an interview setting, the interviewer could provide patients with additional information when needed and could make sure that all the questions were answered. Consequently, there was few missing information when questionnaires could be administered to patients. Furthermore, patients were requested to bring their agenda to the interview (for instance, with information on previous visits to various healthcare professionals) as well as medication prescriptions, which may have had positive consequences for the reliability of cost data collected through patients.

The inclusion and quantification of costs related to productivity losses

All the presented studies were conducted from a societal perspective, i.e. a wide range of costs in and outside the healthcare sector was included in the analyses. This section will specifically focus on costs related to productivity losses. This type of non-medical costs can have a large influence on the total amount of costs in economic studies, also in mental healthcare (23). Over the years, there have been many debates on the inclusion and monetary quantification of productivity losses

due to illness-related absence from work (9). It is widely acknowledged that alternative approaches commonly applied for quantifying productivity losses in economic evaluations may lead to huge differences in estimated costs (24). The human capital approach, for instance, assumes that costs of lost productivity can be estimated by the reduced income of the individual involved. In case of mortality (or permanent incapacity for work), costs are calculated until the retirement age. When using the friction cost method (25), productivity losses are assumed to be confined to the period needed to replace the sick worker. This period is currently estimated at approximately five months in the Netherlands. Not surprisingly, costs of productivity losses are generally much larger when assessed with the human capital approach. It is currently acknowledged that, regardless of the quantification method applied, costs related to productivity losses can be largely overestimated when compensating mechanisms are not taken into account (26). In many situations, for instance, most of the work of people who are (temporary) absent is in practice completed by colleagues during regular working hours. Furthermore, a substantial part of the work can often be compensated by the person involved after returning to work.

In the presented economic evaluations, information was collected on the type of employment, duration of absence, and the return to work after illness-related absenteeism in the patient populations concerned. Results demonstrated that only few patients with chronic schizophrenia (*Chapter 2*) had paid work, and those who did often worked only for a couple of hours per week in sheltered positions. The number of patients who worked part-time (<35 hours per week) was also considerable in the other studies (*Chapters 3-5*), where the proportion of patients with paid work who had a part-time job ranged from 60% to 70%. This is in sharp contrast with 35% part-timers in the regular working population (27). Another aspect concerns the return to work after a period of absence. More than half of the patients with schizophrenia and depression indicated that they gradually increased working hours (often over a period of several months) after absenteeism, before working in accordance with contract hours again. In several studies, initial differences between groups were found in the number of patients with paid work, which complicated the interpretation of productivity costs, especially in the study on DRP. Consequently, a conservative approach to the friction cost method was applied, where sensitivity analyses focused on the in- and exclusion of productivity losses. Conclusions based on the results of these sensitivity analyses were generally comparable to conclusions based on the standard economic analyses conducted in each study.

Currently, a study is being conducted in the Netherlands that focuses on the Individual Placement and Support model for vocational rehabilitation in people

with severe mental illness. Costs related to productivity losses will play an important role in the economic evaluation that is part of the study design. An accompanying HTA methodology study will specifically focus on the quantification of productivity losses in this population, which is expected to lead to adjustments of available approaches that could be applied in other mental healthcare studies as well. These adjustments include a more flexible approach towards the period during which productivity losses are quantified.

Handling missing data in economic evaluations

Results of longitudinal studies can be biased by missing data due to patients who drop out or are lost to follow-up, especially if their missingness is not completely at random (28). The potential bias related to missing data has now also been acknowledged in the area of economic evaluation (29). Economic evaluations in mental healthcare may be confronted with considerable drop-out of patients, as was for instance the case in several recently conducted economic studies focusing on depression in primary care (30).

Various approaches to account for missing data were applied in the studies combined in this thesis. An example of a simple approach is complete case analysis, in which patients with one or more missing measurements are excluded from the analyses. The correctness of applying this form of analysis largely depends on the type of missingness and the amount of missing data. Longitudinal analyses in the HIT study (*Chapter 2*) were in accordance with a complete case approach, 17% of the randomised patients for whom at least one of the measurements was missing were excluded from the analyses. In two of the conducted studies (Cognitive Self-Therapy in *Chapter 3*, discontinuation strategy in *Chapter 5*), mixed model techniques were used for longitudinal analyses of costs and health outcomes. Mixed model techniques use all available information, i.e. also of patients for whom one or more measurements are missing. In the studies on Cognitive Self-Therapy and discontinuation strategy, cost data was complete for, respectively, 79% and 89% of the included patients. In the PEP study (*Chapter 4*), missing data posed a particular problem; for less than half of the included patients with depression could costs be assessed at all the measurements. In this study, the expectation maximisation algorithm with a bootstrap approach was applied. This approach is currently considered to be one of the preferred methods for handling missing cost data (31).

When the number of missing data is limited and missingness appears to be completely at random, methods like complete case analysis may still be valid. However, in many situations analysts will have to apply more advanced approaches. Careful examination of the data, with specific attention to the amount

and pattern of missingness, will provide the information needed to select adequate methods to deal with the problem that incomplete data may pose in various cost studies, also in mental healthcare.

Recommendations for economic evaluations in mental healthcare

Based on the methodological issues discussed above and the findings of the conducted studies, the following recommendations are proposed for future economic evaluations and related research in mental healthcare:

- Cost-effectiveness studies in mental healthcare should apply generic or disease-specific QoL instruments, instead of instruments aimed at specific aspects of health. Various aspects directly related to QALYs, like the validity of instruments from which QALYs are derived, should be adequately assessed in patient populations with mental illness, given current concerns about the use of QALYs in mental healthcare.

- Both the available literature and current findings suggest that in order to perform adequate power analyses, potential effects of interventions should be carefully examined. This is particularly important when using the results of pilot studies. A non-inferiority design seems to be most appropriate for economic studies examining self-help interventions in mental healthcare.

- In order to assess all the relevant economic and clinical consequences of interventions, economic evaluations in mental healthcare should register costs and health outcomes for at least 12 to 18 months. Shorter follow-up periods may lead to incorrect estimations, as indicated by the results of two of the conducted studies. The reliability of cost data could be improved by limiting recall periods of questionnaires to the previous 6 months, or to administer questionnaires on costs by means of face-to-face interviews with the patients, for which patients are requested to bring their agenda.

- Productivity costs can be substantial in mental healthcare and estimates of these costs can vary considerably between commonly applied quantification methods. Initial differences between treatment conditions in the number of patients with paid work may lead to interpretational difficulties, as encountered in this thesis. Based on the current findings, it seems to be highly

relevant to provide decision-makers with information on the consequences of in- and excluding costs related to productivity losses.

- Patient drop-out can be considerable in studies in the area of mental healthcare. Especially studies with long follow-up periods and a large number of assessments over time may be confronted with missing data, as was the case for one of the conducted studies. Various approaches to handle missing data are currently available, which will in many situations be more appropriate than complete case analysis commonly applied in the past.

Closing remarks

The increasing (international) awareness of the burden and costs associated with mental illness has resulted in a growing number of economic evaluations and publications in this field of expertise worldwide. The economic evaluations combined in this thesis provided information to support policy decisions in the Netherlands, and subsequently led to positive reimbursement recommendations for two of the four examined interventions (HIT and Cognitive Self-Therapy). In recent years, several studies conducted in other countries have also demonstrated encouraging clinical and economic results of interventions focusing on mental illness. These interventions could prove to be relevant for the treatment of patients in the Netherlands as well. In the UK, for instance, computerised cognitive behavioural therapy is currently recommended as an evidence based, cost-effective intervention in the treatment of patients with mild to moderate depression and anxiety (32). It seems relevant to compare economic aspects of computerised cognitive behavioural therapy with other self-help strategies, like the CST intervention examined in this thesis (*Chapter 3*). Since there are large differences between countries in the structure of healthcare systems, available regular care, and methods used to assess costs, it is difficult to directly apply results of economic studies conducted in other countries to the situation in the Netherlands, and vice versa. In many cases, detailed (prospective) economic evaluations will have to be conducted in the healthcare system concerned to adequately (re-)evaluate the cost-effectiveness of promising interventions. A recent (model-based) study focused on the economic and clinical consequences of various family interventions in the treatment of patients with schizophrenia in the Australian healthcare system (33). Results suggested that implementation of these interventions in Australia is most likely to be cost-effective. However, it is doubtful whether that will also be the case

for the Netherlands, where family interventions are already more commonly provided by healthcare professionals. Behavioural family treatment was, for instance, one of the treatment options integrated in the HIT intervention described in *Chapter 2*.

Results from studies that did not find differences between economic aspects of alternative interventions are of scientific importance as well, and may prevent other studies from focusing on topics for which there appears to be little room for economic benefits. Several economic evaluations have recently examined the cost-effectiveness of a wide range of interventions for primary care patients with depression in the Netherlands (30). These interventions included two pharmacy-based approaches, a disease management programme, and Interpersonal Therapy. Results indicated that none of the studied interventions was cost-effective in comparison with regular care provided by general practitioners. Conclusions of these studies are comparable to those of the study on PEP (*Chapter 4*) that aimed to prevent recurrences in primary care patients with depression. It seems to be difficult to develop interventions for the treatment of depression that are more (cost-)effective than the care currently provided by GPs.

Although the use of atypical antipsychotics is nowadays widely recommended for the treatment of schizophrenia and first onset psychosis, published economic evaluations demonstrate conflicting results when comparing various (a)typical antipsychotics (34). Detailed economic studies with long term follow-up periods are still frequently initiated to examine the economic aspects of various types of medication in chronic and first onset schizophrenia. It may prove to be worthwhile for economic studies on this topic to start focusing more on subgroups of patients that may benefit from specific types of medication. For instance, the study on alternative medication strategies in first onset psychosis (*Chapter 5*) was unable to find overall differences between guided discontinuation and maintenance treatment. However, a minority of the patients successfully discontinued the use of antipsychotics during the study, without negative economic consequences.

Further implementation of interventions that are proven to be cost-effective is needed to improve the well-being of individuals and to optimise the use of scarce healthcare resources. Unfortunately, the actual implementation of cost-effective interventions in healthcare systems is often complicated (35, 36). The CHOICE programme of the World Health Organization (37) aims to improve the implementation of cost-effective interventions worldwide and illustrates the burden that could potentially be averted. Such initiatives are important in raising awareness among decision-makers about the benefits that can be gained from providing these interventions to patients with mental illness. Presently, the Dutch government stimulates research on various aspects of the implementation of cost-

effective interventions. An ongoing study aims at the implementation of the HIT intervention (*Chapter 2*) in nine mental healthcare centres across the Netherlands. This study additionally tries to identify factors that may either complicate or facilitate the implementation of new interventions in mental healthcare in general.

To conclude, the relevance of detailed economic evaluations to support policy decisions in the area of mental healthcare seems to be widely acknowledged in the Netherlands nowadays. Various psychosocial and psychopharmacological interventions for patients with mental illness were closely examined in economic studies in the last decade, and economic studies of promising interventions in mental healthcare will remain to be important for decision-making in future years. More (research) attention should be focused on the actual implementation of interventions, which is also stimulated by the Dutch government. The availability of cost-effective interventions needs to be improved, so that both society and patients could benefit more fully from the associated economic and clinical advantages.

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Summary

As described in *Chapter 1*, mental disorders are among the most disabling illnesses worldwide, and the associated burden is even expected to increase in coming decades. The studies in this thesis specifically focused on major depressive disorder and schizophrenia, both associated with wide ranging consequences for the lives of patients and their social environment. In addition, the economic consequences of mental illness are substantial as well. It has been estimated that between 2% and 5% of healthcare expenses in Western countries is spent on the treatment of depressive disorders and schizophrenia. In the last decades, decision-makers seem to have become increasingly aware of the burden and rising healthcare costs related to mental illness. Detailed information on economic aspects of interventions in mental healthcare was required for policy decisions. However, this information was practically absent for the Netherlands. The main objective of the studies presented in this thesis was therefore to assess the cost-effectiveness of various interventions focusing on patients with major depressive disorder and schizophrenia in the context of the Dutch healthcare system.

Although there are various treatment options available for people suffering from schizophrenia, most continue to have disabling residual symptoms and remain handicapped in social functioning. Hallucination focused Integrative Treatment (HIT) was developed to improve the well-being of patients with persistent auditory hallucinations by combining various treatment modalities. The cost-effectiveness analysis of HIT presented in *Chapter 2* was an integral part of a clinical study on the effectiveness of HIT in patients with schizophrenia and persistent auditory hallucinations. The study compared two interventions; HIT and care as usual (CAU). Main outcome measure of the cost-effectiveness analysis was the aggregated score on the Positive And Negative Syndrome Scale (PANSS). The study was performed from a societal perspective. Costs and outcomes were registered prospectively during a period of 18 months. In total 63 patients were included in the study, 31 in the HIT group and 32 in CAU. Mean total costs per patient were $18,237 in the HIT group, and $21,436 in the CAU group. Total costs in both groups were largely influenced by the costs of sheltered accommodations and admissions to psychiatric hospitals. Results of the PANSS were more positive for the HIT intervention, but did not differ significantly from CAU. It was indicated that both costs and health outcomes were in favour of HIT, but a statistically significant cost-effectiveness advantage could not be found. Positive outcomes on additional clinical outcome measures could not directly be included in the conducted cost-effectiveness analysis. It was concluded that it seemed most likely that future application of the HIT intervention in patients with chronic schizophrenia would have positive economic consequences.

Many patients suffering from depression and anxiety disorders can not adequately be treated in secondary care due to a limited number of available therapists. Self-therapy interventions appear to be effective for various forms of mental illness and could provide a solution for this healthcare problem. The cost-effectiveness of Cognitive Self-Therapy (CST) in patients with depression and anxiety disorders was assessed in the study described in *Chapter 3*. The economic evaluation was part of an 18-month clinical study on the effectiveness of CST. In total 151 patients were randomly assigned to two intervention arms, CST (n=75) or treatment as usual (TAU, n=76). The economic evaluation was performed from a societal perspective. The primary outcome measure of the cost-effectiveness analysis was the Symptom Checklist 90 (SCL-90). Measurement took place at six-month intervals, starting at the time of inclusion until the end of the follow-up period 18 months later. Results indicated that the mean total costs during the entire study period were €4028 per patient in de CST group and €4837 per patient in de TAU group. Results of the SCL-90 showed improvements in both groups over time, differences between conditions were modest but in favour of CST. Additional analyses indicated that when decision-makers are willing to pay €100 per point improvement on the SCL-90, the probability that CST will be cost-effective increases up to 83%. It was concluded that CST appears to have positive economic consequences and could be applied to relieve the burden of many patients with depression or anxiety disorders who currently do not receive the necessary care due to a limited number of available therapists.

Major depression often runs a chronic-recurrent course and is highly disabling for patients. Recurrence is an important factor contributing to the substantial societal costs associated with depression, but only few (economic) studies specifically focused on the actual prevention of these recurrences. The study described in *Chapter 4* examined the cost-effectiveness of a Psycho-Educational Prevention programme (PEP) aimed at depression in primary care settings in the Netherlands. Patients with depression were randomly assigned to four intervention arms; PEP only, PEP with psychiatric consultation (psychiatrist-enhanced PEP), PEP with cognitive behavioural therapy (CBT-enhanced PEP), and care as usual (CAU). Primary outcome measure in the cost-effectiveness analysis was the proportion of depression-free time. The economic analysis was performed from a societal perspective. Costs and health outcomes were registered at 3-month intervals during a period of 36 months. The Expectation Maximisation algorithm with a bootstrap approach was applied to handle missing data. Longitudinal analyses were based on the data of 226 patients. Mean estimated costs during the 36 months of the study were €8200 in the CAU group, €9816 in the PEP group, €9844 in the psychiatrist-

enhanced PEP group, and €9254 in the CBT-enhanced PEP group. Results of the primary health outcome in the basic PEP condition were worse than in the CAU group. In the psychiatrist-enhanced PEP and CBT-enhanced PEP groups, health outcomes were slightly better. It was concluded that the basic PEP intervention was not cost-effective in comparison with CAU. For the other variants of PEP, costs were higher and health outcomes were only slightly better. Results of this study seem to provide little support for the implementation of PEP in current healthcare systems.

Guidelines for the treatment of first episode psychosis generally recommend maintenance treatment, defined as the prolonged use of antipsychotic drugs following remission. Although this approach appears to be successful in preventing relapses, it is also associated with disabling side effects. Guided discontinuation strategy appears to be less intrusive, but is associated with more relapses. The economic evaluation presented in *Chapter 5* compared the costs and health outcomes of discontinuation strategy with the results of maintenance treatment in patients with first episode psychosis. The included patients were randomly assigned to two treatment conditions, guided discontinuation strategy (n=65) and maintenance treatment (n=63). Subsequently, patients were prospectively followed for 18 months after a period of stable remission. The economic evaluation was conducted from a societal perspective. Quality-Adjusted Life Years (QALYs) were used as primary outcome measure. A wide range of secondary outcomes was also assessed, including relapse rates. Results indicated that there were no relevant differences between groups in terms of mean total costs during the main study phase of 18 months. Furthermore, no differences between groups were found for QALY results. The relapse rate in the discontinuation strategy group (42%) was twice as high as in maintenance treatment (21%). Discontinuation strategy did not lead to the advantages that were expected on other secondary outcomes. It was concluded that there were no indications that either of the examined medication strategies in first episode patients is superior to the other in terms of economic outcomes. For a minority of remitted first episode patients, guided discontinuation strategy could form a feasible alternative to maintenance treatment.

It is generally recommended to use preference-based health outcomes in economic evaluations, in particular Quality-Adjusted Life Years (QALYs). However, by far the most economic studies in mental healthcare were designed as cost-effectiveness analyses focusing on a specific aspect of health. *Chapter 6* demonstrated the potentially negative consequences of (arbitrarily) choosing between outcome measures in mental healthcare. Data collected in the context of the HIT study

(*Chapter 2*) was used for illustrative purposes. Economic analyses based on the initially selected single primary health outcome were compared to analyses based on various other relevant health outcomes assessed during the study, including social functioning, quality of life, and QALYs. Relevant and significant differences were identified on three of the four additionally assessed health outcomes, in contrast to moderate differences on the originally selected primary outcome. Cost-effectiveness analyses and acceptability curves were more strongly in favour of the HIT intervention when focusing on these three additional instruments. However, QALY results did not show relevant differences between groups, nor did additional economic analyses based on this outcome. It was concluded that the selection of a single primary outcome measure in cost-effectiveness analysis may lead to various problems in the field of mental healthcare. Decision-makers could be provided with incomplete and eventually incorrect information. It was suggested to use (disease-specific or generic) QoL instruments for assessing health outcomes in studies where the described problems may arise, at least until there is consensus on a valid preference-based instrument suited for mental healthcare.

In *Chapter 7*, an overview was provided of the main findings of the presented studies. Two of the four examined interventions were eventually recommended for reimbursement in the Dutch healthcare system. Furthermore, various methodological issues that seem highly relevant for economic evaluations in mental healthcare were discussed. These included the use of QALYs versus (disease-)specific outcome measures, power analyses and alternative study designs, length of follow-up periods, inclusion and quantification of productivity losses, and handling missing data in economic studies. Several suggestions for the design of economic evaluations in mental healthcare were formulated based on the discussed methodological issues. Recent (inter)national developments and outcomes of various other interventions studied in mental healthcare were discussed in light of the present findings. It seems that more (research) attention should be focused on the actual implementation of cost-effective interventions in mental healthcare, to optimise associated economic and clinical benefits for both society and patients involved.

Samenvatting

Psychiatrische aandoeningen behoren wereldwijd tot de meest invaliderende en ernstige ziektebeelden, en de hiermee gepaard gaande ziektelast zal naar verwachting zelfs verder toenemen in de komende jaren. De studies die deel uitmaken van dit proefschrift richtten zich specifiek op depressie en schizofrenie. Deze aandoeningen hebben verregaande consequenties voor zowel de patiënten zelf als voor mensen in hun directe omgeving. Daarnaast is er ook sprake van aanzienlijke economische gevolgen voor de maatschappij. Naar schatting wordt momenteel tussen de 2% en 5% van de gezondheidsuitgaven in Westerse landen besteed aan de behandeling van depressie en schizofrenie. In de afgelopen jaren lijken beleidsmakers zich in toenemende mate bewust te zijn geworden van de ziektelast en stijgende kosten als gevolg van psychiatrische aandoeningen. Gedetailleerde informatie over economische aspecten van alternatieve behandelingsvormen voor psychiatrische aandoeningen was echter nagenoeg niet voorhanden in de Nederlandse situatie. Het doel van de studies die deel uitmaken van dit proefschrift was dan ook om de kosteneffectiviteit vast te stellen van verschillende interventies gericht op patiënten met depressie of schizofrenie in de context van de Nederlandse gezondheidszorg.

Ondanks de verschillende behandelopties die beschikbaar zijn voor patiënten die lijden aan schizofrenie, blijft het merendeel van de patiënten last houden van restsymptomen en beperkingen in het sociaal functioneren. De HIT interventie (op Hallucinaties gerichte Integratieve Therapie) werd ontwikkeld om het welzijn van patiënten met gehoorshallucinaties te verbeteren door middel van het combineren van verschillende behandelingsvormen. In *hoofdstuk 2* werden de resultaten gepresenteerd van de kosteneffectiviteitsanalyse gericht op HIT in een patiëntenpopulatie met schizofrenie en therapieresistente gehoorshallucinaties. In deze studie werden twee behandelcondities met elkaar vergeleken; HIT en care as usual (CAU: reguliere zorg). Primaire uitkomstmaat in de kosteneffectiviteits-analyse was de totaalscore op de PANSS (Positive And Negative Syndrome Scale). De economische evaluatie werd vanuit een maatschappelijk perspectief uitgevoerd. Kosten en gezondheidsuitkomsten werden prospectief geregistreerd gedurende een periode van 18 maanden. In totaal werden 63 patiënten geïncludeerd, waarvan 31 patiënten random aan de HIT groep werden toegewezen en 32 aan CAU. De gemiddelde totale kosten per patiënt bedroegen $18.237 in de HIT groep en $21.436 in de CAU groep. De omvang van de totale kosten werd in beide groepen in aanzienlijke mate bepaald door de kosten die gepaard gingen met opnames in psychiatrische ziekenhuizen en verblijf in Beschermde Woonvormen. Resultaten op de PANSS waren in het voordeel van de HIT interventie, maar verschillen tussen groepen waren niet statistisch significant. Resultaten op het gebied van

zowel kosten als gezondheidsuitkomsten gaven aan dat HIT tot positievere resultaten leidde dan CAU, maar er was geen sprake van een statistisch significant voordeel qua kosteneffectiviteit. Positieve uitkomsten op secundaire uitkomstmaten konden niet direct worden meegenomen in de uitgevoerde kosteneffectiviteits-analyse. Er werd geconcludeerd dat het waarschijnlijk is dat het toepassen van HIT bij de doelpopulatie met positieve economische gevolgen gepaard zal gaan.

Een aanzienlijk deel van de patiënten met depressie en angststoornissen kan niet adequaat worden behandeld als gevolg van een beperkt aantal beschikbare behandelaars in de tweedelijnszorg. Zelftherapie behandelingsvormen lijken effectief te zijn voor verschillende psychiatrische aandoeningen en zouden een oplossing voor dit probleem kunnen vormen. De studie die wordt beschreven in *hoofdstuk 3* richtte zich op de kosteneffectiviteit van Cognitieve Zelfherapie (CZT) bij patiënten met depressie en angststoornissen. De economische evaluatie maakte deel uit van een 18 maanden durende klinische studie gericht op de effectiviteit van CZT. In totaal werden 151 patiënten random toegewezen aan twee behandelings-armen; CZT (n=75) en TAU (treatment as usual: reguliere behandeling, n=76). De economische evaluatie werd uitgevoerd vanuit een maatschappelijk perspectief. Primaire uitkomstmaat in de kosteneffectiviteitsanalyse was de SCL-90 (Symptom Checklist 90). Metingen vonden vanaf het moment van inclusie om de 6 maanden plaats, waarbij de laatste meting 18 maanden na inclusie werd uitgevoerd. De gemiddelde totale kosten per patiënt bedroegen €4028 in de CZT groep en €4837 in de TAU groep. Resultaten van de analyses gericht op de SCL-90 gaven aan dat beide patiëntengroepen over de tijd verbeterden. Verschillen tussen de SCL-90 uitkomsten van beide groepen waren licht in het voordeel van de CZT groep. Aanvullende analyses lieten zien dat indien beleidsmakers bereid zijn om €100 per punt verbetering op de SCL-90 te betalen, de waarschijnlijkheid dat CZT kosteneffectief zal zijn toeneemt tot 83%. Op basis van deze bevindingen werd geconcludeerd dat CZT positieve economische consequenties lijkt te hebben, en daarom toegepast zou kunnen worden in de behandeling van patiënten met depressie en angststoornissen die momenteel onvoldoende zorg ontvangen door een tekort aan behandelaars.

Depressie toont vaak een chronisch-recidiverend beloop en kan een grote invloed op het leven van patiënten hebben. Het recidiverende karakter draagt in belangrijke mate bij aan de aanzienlijke maatschappelijke kosten van depressie. Desondanks heeft slechts een beperkt aantal economische studies zich specifiek gericht op recidief preventie bij depressie. De studie in *hoofdstuk 4* onderzocht de kosteneffectiviteit van een programma gericht op het voorkomen van recidieven bij

patiënten met depressie in de eerstelijnszorg (PEP: Psycho-Educatief Preventie Programma). Patiënten met depressie werden random toegewezen aan vier interventiearmen; PEP, PEP met psychiatrische consultatie (PC+PEP), PEP met cognitieve gedragstherapie (CBT+PEP), en gebruikelijke zorg door de huisarts (CAU; care as usual). Primaire uitkomstmaat in de kosteneffectiviteitsanalyse was de proportie depressievrije tijd. De economische evaluatie werd uitgevoerd vanuit een maatschappelijk perspectief. Kosten en gezondheidsuitkomsten werden driemaandelijks vastgesteld gedurende een periode van 3 jaar. Missende waarden werden ondervangen met behulp van het EM algoritme in combinatie met een bootstrap benadering. Longitudinale analyses waren gebaseerd op de gegevens van 226 patiënten. De gemiddelde kosten tijdens de studieperiode van 3 jaar bedroegen €8200 in de CAU groep, €9816 in de PEP groep, €9844 in de PC+PEP groep, en €9254 in de CBT+PEP groep. Resultaten op de primaire uitkomstmaat waren slechter voor de PEP groep dan voor de CAU groep. Voor zowel de PC+PEP als de CBT+PEP groep waren de uitkomsten op de primaire uitkomstmaat enigszins beter dan voor de CAU groep. Er werd geconcludeerd dat PEP niet kosteneffectief is in vergelijking met de gebruikelijke zorg verleend door huisartsen. De uitgebreide varianten van PEP gingen gepaard met hogere kosten en enigszins betere gezondheidsuitkomsten. De resultaten van deze studie lijken weinig ondersteuning te bieden voor het implementeren van PEP in de Nederlandse gezondheidszorg.

Richtlijnen voor de behandeling van patiënten met een eerste psychotische episode raden over het algemeen onderhoudsbehandeling aan, bestaande uit het langdurig voorschrijven van antipsychotica. Hoewel deze behandelwijze succesvol lijkt te zijn in het voorkomen van terugval, krijgen patiënten vaak te maken met belemmerende bijwerkingen. Kortdurende medicamenteuze behandeling, gericht op het begeleid afbouwen en discontinueren van antipsychotica, lijkt positieve gevolgen voor het functioneren van patiënten te hebben, maar zou met een hogere kans op terugval gepaard kunnen gaan. In *hoofdstuk 5* werden de kosten en gezondheidsuitkomsten vergeleken tussen de onderhoudsbehandeling en kortdurende medicamenteuze behandeling bij patiënten met een eerste psychotische episode. In totaal werden 128 patiënten random toegewezen aan een van beide behandelwijzen; langdurige onderhoudsbehandeling (n=63) of een kortdurende medicamenteuze behandeling (n=65). Patiënten werden prospectief gevolgd gedurende 18 maanden na een periode van stabiele remissie. De economische evaluatie werd uitgevoerd vanuit een maatschappelijk perspectief. QALYs (voor kwaliteit gecorrigeerde levensjaren) werden gebruikt als primaire uitkomstmaat in de economische analyses. Verschillende secundaire uitkomsten werden vastgesteld, waaronder terugvalpercentages. De resultaten lieten zien dat er

geen relevante verschillen tussen de groepen waren op het gebied van kosten. Ook voor de QALY resultaten werden geen verschillen gevonden. Het terugvalpercentage was in de groep die kortdurend werd behandeld twee keer zo groot (42%) dan in de onderhoudsgroep (21%). Kortdurende medicamenteuze behandeling leidde niet tot de verwachte voordelen op de overige uitkomstmaten. Er waren geen aanwijzingen dat één van de onderzochte behandelstrategieën voor patiënten met een eerste psychose superieur was ten opzichte van de ander qua economische bevindingen. Voor slechts een minderheid van de patiënten die hersteld zijn van een eerste psychose zou kortdurend medicatiegebruik een reëel alternatief voor onderhoudsmedicatie kunnen vormen.

Richtlijnen voor economische evaluaties raden over het algemeen aan om gebruik te maken van generieke (utiliteitsgebaseerde) uitkomstmaten, zoals de QALY (voor kwaliteit gecorrigeerde levensjaren). Veruit de meeste gepubliceerde economische evaluaties op het gebied van de geestelijke gezondheidszorg (GGz) werden echter opgezet als kosteneffectiviteitstudies die zich richtten op een specifiek gezondheidsaspect. *Hoofdstuk 6* liet zien wat de negatieve gevolgen kunnen zijn van het kiezen tussen verschillende uitkomstmaten in kosteneffectiviteitstudies op het gebied van de psychiatrie. De gegevens uit de HIT studie (*hoofdstuk 2*) werden gebruikt ter illustratie van de betreffende problemen. Economische analyses gebaseerd op de oorspronkelijk gekozen primaire uitkomstmaat werden vergeleken met de resultaten van analyses gebaseerd op andere uitkomsten die tijdens de studie werden gemeten, waaronder sociaal functioneren, kwaliteit van leven en QALYs. Relevante en significante verschillen werden gevonden op drie van de vier aanvullend afgenomen uitkomstmaten, dit in tegenstelling tot de beperkte verschillen op de primaire uitkomstmaat. Resultaten van de economische analyses gebaseerd op deze drie uitkomstmaten waren sterk in het voordeel van de HIT interventie. Er werden echter geen relevante verschillen voor QALY resultaten gevonden. Op basis van deze bevindingen werd geconcludeerd dat het kiezen tussen uitkomstmaten tot problemen kan leiden voor kosteneffectiviteitsanalyses op het gebied van de GGz. Beleidsmakers kunnen hierdoor onvolledige, en mogelijk ook onjuiste informatie aangeleverd krijgen. Er werd aangeraden om voorlopig gebruik te maken van (generieke of ziektespecifieke) kwaliteit van leven vragenlijsten voor het vaststellen van gezondheidsuitkomsten in studies waar de genoemde problemen zich zouden kunnen voordoen. Er zal uiteindelijk geprobeerd moeten worden om consensus te bereiken over een valide en betrouwbaar utiliteitsinstrument dat geschikt is voor afname bij patiënten met psychiatrische aandoeningen.

In *hoofdstuk 7* werd een overzicht gegeven van de voornaamste bevindingen van de beschreven studies. Twee van de vier onderzochte interventies kwamen uiteindelijk in aanmerking voor vergoeding in de context van de Nederlandse gezondheidszorg. Daarnaast werden verschillende methodologische aspecten besproken die relevant zijn voor het uitvoeren van economische evaluaties op het gebied van de GGz. Deze aspecten bestonden uit het gebruik van QALYs versus (ziekte-)specifieke uitkomstmaten, power analyses en alternatieve studie opzetten, de duur van follow-up periodes, de inclusie en waardering van productiviteitsverliezen, en het omgaan met patiëntenuitval. Op basis van de besproken methodologische aspecten werden suggesties gedaan voor de opzet van toekomstige economische evaluaties binnen de GGz. Verschillende recente (inter)nationale ontwikkelingen en resultaten van andere onderzochte interventies werden besproken in het licht van de huidige bevindingen. Er lijkt meer onderzoek nodig te zijn op het gebied van de daadwerkelijke implementatie van kosteneffectieve interventies binnen de GGz, om de hiermee gepaard gaande economische en klinische voordelen te optimaliseren voor zowel de maatschappij als de betreffende patiënten.

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About the author

Dennis Stant was born on the 20th of July 1974 in Deventer, and grew up in the picturesque town of Holten, the Netherlands. He studied Psychology at the University of Groningen and graduated in 1999. His interest in diverse research areas led to a position at the Office for Medical Technology Assessment of the University Medical Center Groningen in 2000. Over the years, the author has been involved in various research projects in the Dutch healthcare system. These studies generally focused on clinical and economic aspects of interventions for patient populations with mental illness, in particular schizophrenia and major depressive disorder. However, his research experience also includes a variety of other topics and projects, ranging from studies on the quality of life of childhood cancer survivors to the implementation of interventions in mental healthcare institutions. The author is currently living in Groningen, together with his girlfriend.